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SPECIAL LISTING

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CURRENT CANCER RESEARCH

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BREAST CANCER: DIAGNOSIS, PROGNOSIS, AND TREATMENT

DECEMBER 11, 1980

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health •
National Cancer Institute

A SERVICE OF THE
INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB)

Dear Cancer Researcher:

This **SPECIAL LISTING** of Current Cancer Research Projects is a publication of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) Program of the National Cancer Institute. Each **LISTING** contains descriptions of ongoing projects in one selected cancer research area. Approximately 50 different cancer research areas are covered by a separate **SPECIAL LISTING**.

The present series of **SPECIAL LISTINGS** is a third edition, and begins with number 201. This series will update the second edition which included **SPECIAL LISTINGS** numbered 101 through 147. Depending on the total number and types of cancer research summaries received, the third edition will have at least 47 titles, and possibly a few more. In most cases, each third edition **SPECIAL LISTING** will replace the exact subject area of a second edition **LISTING** (SL 201 replacing SL 101, etc.). Whenever the number and variety of summaries requires a change in this procedure, a notation will be made in the specific **LISTINGS** affected.

The purpose of these **LISTINGS** is to promote and facilitate the exchange of information among cancer scientists. The project descriptions in the **LISTINGS** are provided by cancer scientists from more than 50 different countries. Researchers are urged to prepare accurate summaries which will be rapidly processed for inclusion in the CANCERPROJ data base as well as future **SPECIAL LISTINGS**.

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CURRENT CANCER RESEARCH

I. IMAGING AND OTHER TECHNIQUES IN DETECTION AND DIAGNOSIS OF BREAST CANCER

A. ULTRASONOGRAPHY IN DIAGNOSIS OF BREAST CANCER

1. USE OF ULTRASOUND IN THE DIAGNOSIS OF BREAST CANCER

Taylor, K. J., Peck, D., Yale University, School of Medicine, Dept. of Radiology, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

A new ultrasound scanner is available which combines automation with high resolution and digital format for display. Financial support is requested to perform a clinical evaluation of this instrument. It is proposed that we scan at least 2500 women over a period of two years. These results will be compared with the xeroradiographic findings, clinical examination and surgical and pathological follow-up on patients proceeding to surgery. This will enable us to determine both the sensitivity and specificity of ultrasound examination of the breast compared with conventional imaging methods and clinical examination. It is also proposed that the acoustic parameters of normal and abnormal tissue will be quantized using computerized facilities which will be available by late 1978.

The advantages of ultrasound imaging are its lack of ionizing radiation, its non-invasiveness, and its capacity, not yet fully exploited, to obtain high resolution in superficial organs. We believe that this project will help to realize the earlier diagnosis of breast disease without the use of ionizing radiation.

2. USE OF ULTRASOUND IN DIAGNOSIS OF BREAST CANCER

Goldberg, B. B., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiology, *1025 Walnut St., Philadelphia, Pennsylvania,* 19107, United States of America

The purpose of this proposal is to define a method for the development of a non-invasive ultrasonic technique for the diagnosis of malignant breast disease; and ultimately, to test this application as a screening tool, using a sample population of asymptomatic at risk women.

3. BREAST DIAGNOSIS QUANTITATIVE IMAGING BY ULTRASOUND

Greenleaf, J. F., Bahn, R. C., Hattery, R. R., Mayo Foundation, Ultrasound Research Laboratory, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

The goal of this proposal is to construct a clinically reliable ultrasound scanner which can obtain quantitative images of several acoustical parameters within two-dimensional cross-sections of the breasts of patients in a period of a few minutes. The instrument will combine these quantitative multimodal images to obtain a synergistic effect resulting in a high probability of obtaining differential diagnosis of breast disease. Ultrasound computer-assisted transmission tomography will be utilized to obtain quantitative cross-sectional images of acoustic speed, acoustic attenuation, acoustic absorption and scatter and reflection where appropriate. Synthetic aperture imaging and compound B-scan techniques will be utilized to obtain high resolution images of the distribution of echoing interfaces within each studied plane of the breast. Aberrations in the images caused by inhomogeneous distributions of acoustic speed will be corrected by techniques currently under development in this laboratory. A clinical trial will be conducted in which patients scheduled for surgical biopsy will be scanned by the ultrasound scanner and the resulting images compared to the results of the biopsy and/or surgical mastectomy. Comparisons between surgical specimens and acoustic images will be made using methods of automated computer-assisted pattern classification and recognition combined with histological methods of tissue preparation specifically designed to aid in comparing the ultrasound images of the coronal plane of the intact breast with similar planes through the excised breast. This parallel development of the clinical instrument, the tissue analysis technique, and the pattern recognition programs should result in complete evaluation of a prototype clinical instrument which could be used in the high volume clinical environment.

BIBLIOGRAPHIC REFERENCES: Kenue, S. K. and Greenleaf, J. F.: High speed convolving kernels for CT having triangular spectra and/or binary values. IEEE Transactions on Nuclear Science, NS-26(2):2693-2696 (April) 1979. Kenue, S. K. and Greenleaf, J. F.: Efficient convolution kernels for computerized tomography. Ultrasonic Imaging, 1:232-244, 1979.

4. BREAST TUMOR DIAGNOSIS BY COMPUTED ULTRASOUND

Swindell, W., Haber, K., Barrett, H. H., Bartels, P. H., University of Arizona, School of Medicine, Dept. of Radiology, *1501 N. Campbell Ave., Tucson, Arizona,* 85721, United States of America

Proposed research is to apply computed ultrasound to breast cancer diagnosis. Using special transducers and powerful pattern recognition computer programs we will collect clinical data and search for highly discriminating echo features and classification rules. The major goals are to (1) obtain characteristic features of digitized ultrasound signals scattered from breast tumors in order to (2) determine classification rules and error probabilities for quantitative computer diagnosis and (3) accumulate data base for use in evaluating use of methods in ultrasonic breast cancer screening programs.

5. ULTRASONIC COMPUTED TOMOGRAPHY OF BREAST CANCER

Carson, P. L., Johnson, M. L., Scherzinger, A., Meyer, C., Gerner, R. E., Silverberg, S., Kuni, C., Moore, G., Clark, D., Jobe, W., University of Colorado, Medical Center, School of Medicine, Dept. of Radiology, *4200 E. 9th Ave., Denver, Colorado,* 80262, United States of America

A system for ultrasonic computed tomography of attenuation and speed of ultrasound propagation along with simultaneous pulse echo imaging of the same plane has been developed during investigations under a four year NSF grant. Use of moderately large, focused transducers has minimized refraction artifacts in attenuation images and provided high resolution in pulse echo and attenuation images of the breast. Use of the small transducer area utilized by others has provided state-of-the-art velocity images. Initial design studies on patients and normal volunteers have allowed development of images with surprising detail and have revealed the complementary relations between ultrasonic attenuation and velocity images.

Clinical trials of noninvasive breast cancer diagnosis with ultrasonic computed tomography of attenuation and velocity in comparison with pulse echo ultrasound and other imaging modalities have been initiated. Approximately 180 patients will be imaged in the project with ultrasonic CT and pulse echo imaging in the same planes as the UCT to be added in the second year. Most patients will be those in which carcinoma is indicated strongly or in which mammography suggests a small mass. Double blind studies of interpretation of UCT and pulse echo ultrasound, x-ray and a few cases of microwave mammography will be conducted as will extensive histopathologic correlation.

Development of both improved phase dependent and phase independent imaging of ultrasonic attenuation as well as development of more accurate velocity imaging is planned.

BIBLIOGRAPHIC REFERENCES: Lambert, P.A., Carson, P.L., Dick, D.E., Oughton, T.V., and Kubitschek, J.E., 1979. Improvements in Ultrasonic CT Data Acquisition and Preprocessing, Proc. IEEE-EMBS Conf. Frontiers of Engineering in Health Care, Oct. 6-7, 1979, in press. Jones, S.M., Kitsen, F.L., Carson, P.L., and Bayly, E.J., 1979. Investigation of Phase Incoherent and other Signal Processing With a Simulated Array for Ultrasonic CT. Proc. IEEE-EMBS Conf. Frontiers of Engineering in Health Care, Oct. 6-7, 1979, in press.

6. ULTRASOUND MAMMOGRAPHY

Baum, G., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Ophthalmology, *1300 Morris Park Ave., Bronx, New York*, 10461, United States of America

The goal of this phase of the project is to: 1) refine the ultrasonographic criteria so that non-palpable breast cancers can be detected, 2) reduce the volume of data that has to be recorded, read and analyzed by improved methods of tumor localization, 3) develop the algorithms for digital analysis of the acoustic texture of tissues. Digital data compression, image enhancement, on-line signal processing, alternate display techniques and the feasibility of computer sorting are to be explored to solve these problems. All B-mode ultrasonography and X-ray computerized axial tomography share these problems so that the solutions developed in this research program have universal application for cancer detection throughout the body.

An ultrasound mammography study we have already conducted has shown that palpable scirrhus carcinomas of the breast produce an acoustic area that contains weak echoes which are very absorbent.

The problem is locating the small volume of tissue characteristic of the tumor in the comparatively large volume of breast tissue and then proving that the chosen volume is the malignant tumor.

Serial scanned ultrasound mammography at 3.0 mm intervals produced by the new breast ultrasonoscope will be analyzed. This interpretation will be correlated with the pathological, clinical, surgical and X-ray findings. The ultrasonograms will then be used to form three-dimensional ultrasonograms and digitized for textural analysis.

7. ULTRASOUND STUDIES

Hunt, J. W., Foster, S., Taylor, W. B., Hill, R. P., Ontario Cancer Inst., Physics Division, *500 Sherbourne St., Toronto, Ontario*, M4X 1K9, Canada

OBJECTIVE: Improved diagnosis, with special emphasis on breast ultrasound scanning.

APPROACH: Ultrasound techniques to obtain high-quality tomographic images.

PROGRESS: a) The general basic ultrasound transmission studies indicate that improved resolution can be obtained by using a high-aperture transducer to focus the beam through human tissue. b) The depth of field of a sharply focussed beam is extremely poor for traditional systems. This has been improved by a special annular ring transducer, coupled with a variable focus so that a good focus over the whole field is achieved. In a second technique a unique cylindrical scatter scanner has been designed by Dr. Foster in our laboratory. Here, a cylindrical shaped transducer generates a sharp line focus. A second transducer, in-line with this focus, detects the scattered waves. The system scans in the same way as a normal ultrasound system. Very high-resolution images have been obtained. c) A simple breast scanner is now being used clinically and two new high-resolution systems are being completed. We hope that these improved designs will provide good diagnostic accuracy in case of breast cancer, with little risk to the patient.

8. DETECTION OF BREAST CANCER BY ULTRASONIC DOPPLER BLOOD FLOW SIGNALS

Wells, P. N., Halliwell, M., Bristol General Hospital, Dept. of Medical Physics, *Bristol BS1 6SY, England, United Kingdom*

OBJECTIVE: To determine the feasibility of developing a rapid scanner for screening for breast cancer by the ultrasonic detection of abnormal blood flow.

APPROACH: Preliminary experiments have demonstrated that the abnormal blood flow, associated with malignant tumor neovascularisation, produces characteristic ultrasonic Doppler singnals. The possibility of detecting these signals in breast cancer by means of an automatic water-bath-coupled ultrasonic scanner is being investigated, and the physics of the origin of the signals is being studied.

PROGRESS: A library of breast Doppler signals is being collected, using a hand-held skin-contact probe. Methods of characterizing the singnals, including frequency spectrum analysis, are being investigated. A two-dimensional pulse-eco breast scanner is being constructed.

9. DEVELOPMENT OF ULTRASONIC BREAST TISSUE PHANTOM

Zagzebski, J. A., Madsen, E. L., University of Wisconsin, Madison Campus, Medical School, Depts. of Radiology/Human Oncology, *307 N. Charles St., Madison, Wisconsin*, 53706, United States of America

The objective of this proposal is to design, construct and evaluate ultrasonic tissue-equivalent phantoms of the breast. The purpose of the work is to create standardized objects with realistic acoustic structures and targets for assessing imaging capabilities of state-of-the art ultrasonic breast scanning equipment. Phantoms will be constructed using tissue equivalent gels for mimicking various breast constituent tissues.

Designs for phantoms are based upon anatomical sections of breast tissue, available in our laboratory as well as in the literature. Further developmental work on the phantom material is proposed, primarily in order to match small particle scattering with scattering observed in breast tissues. A major portion of the effort is devoted to the development of construction techniques for the incorporation of structures of sufficient geometric complexity to provide acoustic interfaces and mimicked tissue volumes which are representative of those encountered in vivo. Evaluation of phantoms is being carried out in part in laboratories where advanced ultrasonic breast imaging systems are being designed and employed.

10. IMPROVEMENT OF DIAGNOSTIC MEDICAL IMAGING

Johns, H. E., Bronskill, M. J., Hunt, J. W., Battista, J. J., Ontario Cancer Inst., Physics Division, *500 Sherbourne St., Toronto, Ontario*, M4X 1K9, Canada

The physics of various diagnostic imaging techniques is being investigated in order to improve existing imaging techniques and to develop new imaging modalities. A) Ultrasound: The absorption and attenuation characteristics of normal and tumor tissues are being measured with the intent of distinguishing between tissue types by using ultrasound. Various techniques for focussing wide-aperture transducers are being developed for the specific purpose of designing and constructing an ultrasound breast scanner to screen for breast cancer. B) Nuclear Medicine: Electronic and image processing techniques are being used in conjunction with conventional scintillation cameras to: 1) Reduce image degradation by respiratory motion in liver scintigraphy, 2) locate accurately and quantify radionuclide uptake in lymph nodes imaged by internal mammary lymphoscintigraphy, 3) optimize detection efficiency by improving display systems and recording films. C) CT Scanners: X-ray sources, beam filters, radiation detectors and reconstruction algorithms are being investigated in order to obtain better tissue characterization using third and fourth generation CT scanners. The use and optimization of CT scanner images in radiation therapy dose calculation is under way. D) Comparison of modalities: preliminary data collection and analysis is being applied to the comparison of overlapping imaging techniques in an attempt to develop clinically useful protocols or decision trees for specific types of cancer patients.

11. CANCER HYPERTHERMIA THERMOMETRY BY ULTRASOUND

Johnson, S. A., Christensen, D. A., Anderson, R. E., Berggren, M. J., Utah Higher Education System, University of Utah, School of Engineering, Dept. of Bioengineering, *1400 E. 2nd S., Salt Lake City, Utah*, 84112, United States of America

An instrument is proposed for noninvasive mapping of internal body temperatures during hyperthermia cancer therapy. This instrument may provide a means to control the temperature and distribution of heat applied by microwave or applied by heating ultrasound radiation. The instrument relies upon the

temperature dependent speed of ultrasound in tissues, from which temperature may be reconstructed by tomographic techniques. Accurate calibration will be assured by including one or more of the latest available invasive point temperature probes within the instrument's field of view. Evaluation of the method will involve laboratory tests on artificial models, phantoms, and excised tissue samples, after which the prototype instrument will be evaluated using animals (such as young pigs) and, perhaps later, volunteer humans. Further tests will be conducted on a second generation scanner designed for imaging more difficult parts of the body such as the limbs, the neck, and the abdomen, where bone or gas may limit the field of view or cause troublesome reflection or refraction.

BIBLIOGRAPHIC REFERENCES: E.L. Ritman, R.A. Robb, S.A. Johnson, P.S. Chevalier, B.K. Gilbert, J.F. Greenleaf, R.E. Sturm, and E.H. Wood, Quantitative Transaxial Imaging of the Anatomic Structure and Function of the Heart, Lungs, and Circulation. Mayo Clinic Proceedings, Vol. 53, p. 38, 1978. J.F. Greenleaf, S.A. Johnson, and A.H. Lent, Measurement of Spatial Distribution of Refractive Index in Tissues by Ultrasonic Computer Assisted Tomography, Ultrasound in Medicine and Biology, Vol. 3, pp. 327-339, 1978.

12. SCANNING ACOUSTIC MICROPROBE FOR CANCER DIAGNOSIS

Barber, F. E., Sonnenfeld, M., Sletzinger, L., Harvard University, Boston Campus, School of Medicine, Dept. of Radiology, *25 Shattuck St., Boston, Massachusetts*, 02115, United States of America

A new method has been developed for imaging the fine structure of human tissues called a scanning acoustic microprobe. The system detects, on a scale of a fraction of a millimeter resolution, the isotropic scattering strength, directive scattering strength, directivity, and relative attenuation of tissues at each point in the image plane. By computer graphics an image is reconstructed using these parameters. The method will be used initially for differential diagnosis of breast tumors and for following the course of therapy. The data acquisition system, data processing and pattern recognition system, and the reconstruction system are all based on original and proven concepts for pulse-echo ultrasonic tissue characterization and imaging.

The microprobe should have general applicability to diagnosis in other organs of the body, as well as the breast.

B. THERMOGRAPHY IN DIAGNOSIS OF BREAST CANCER

13. SCREENING FOR NEOPLASMS IN IRRADIATED POPULATIONS

Hempelmann, L. H., Woodard, E., Shore, R., Rogoff, R., University of Rochester, School of Medicine & Dentistry, Dept. of Radiology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

This population of 606 women treated with x-rays for acute post-partum mastitis and their controls (554 sisters; 539 women with post-partum mastitis not treated with x-rays, and their 206 sisters) have been followed by mail questionnaire since 1955. The irradiated women have an increased risk of developing breast cancer. This application proposes continuation of the mail health survey, the review of histopathology of the breast cancers experienced by the treated women and the controls, and periodic mammograhic-thermographic screening of the treated women and eligible controls (NCI guidelines).

14. SCREENING FOR DETECTION OF BREAST CANCER

Gilbert, F. I., Pacific Health Research Inst., *Alexander Young Bldg., Suite 542, Honolulu, Hawaii*, 96813

One year renewal of Breast Cancer Detection Demonstration Project. Contractor will continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women will continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination - in accordance with the contract statement of work, and NCI/ACS issued screening guidelines.

15. DATA MANAGEMENT CENTER FOR BREAST CANCER DETECTION

Foradori, G., University City Science Center, *3624 Market St., Philadelphia, Pennsylvania*, 19104, United States of America

Contractor will continue to rescreen as many as possible of an original number of ten thousand women participating in this projet. These women will continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination - in accordance with the contract statement of work and NIC/ACS issued screening guidelines.

C. RADIO-MAMMOGRAPHY AND RELATED TECHNIQUES IN DETECTION OF BREAST CANCER

16. EVALUATION OF PERIODIC BREAST CANCER SCREENING WITH MAMMOGRAPHY AND CLINICAL EXAMINATION

Venet, W., Shapiro, S., Strax, P., Venet, L., Fink, R., Health Insurance Plan of Greater New York, Dept. of Research & Statistics, *625 Madison Ave., New York, New York*, 10022, United States of America

This is a randomized trial designed to test whether periodic screening with clinical and mammographic examinations results in a long-term reduction in breast cancer mortality. Linked to this primary objective are several issues of major importance in assessing benefits to be derived from breast cancer screening, e.g., the relative value of the two screening modalities, ages of women to be screened, periodicity of screening, identification of parameters related to development of the disease, and determinations of underlying cause of death. Approximately 62,000 women, aged 40-64 at the time of entry to the study and allocated to either a study or a control group, are under surveillance. Study women were offered screening examinations; of the 65 percent who accepted an initial examination, a large majority had at least one of the three additional screenings at annual intervals. Control women continued to receive their regular medical care. Screening ended in mid-1970, and follow-up on the entire study and control populations for breast cancer cases and death ascertainment continues. The survival status of all known breast cases through December of 1977 has been established, and no one is lost to follow-up. New data support earlier results on screening benefits. At ten years of follow-up from entry, a 30 percent differential exists between the total study (screenees and refusers) and control group in breast cancer mortality. The impact of the screening program continues to be confined to women 50 years of age and over with no benefit at ages 40-49. Eight year case fatality rates show similar relationships. The differential between control and study cases is due almost entirely to the low rates among cases detected through screening, with cases detected through mammography alone showing a rate that is exceptionally low. At this point in the study there appears to be strong support for periodic screening at ages 50 years and over with the two modalities.

17. STUDY OF VALUE OF MAMMOGRAPHY

Venet, W., Health Insurance Plan of Greater New York, *625 Madison Ave., New York, New York*, 10022, United States of America

OBJECTIVE: Retrieve information obtained from screening, not yet coded, and from women's study charts to aid the National Cancer Institute's Division of Cancer Biology and Diagnosis in relating blood sample information to report on women who had benign biopsies. This will require retrieving charts from storage and coding chart information from computer storage for blood samples which were drawn from about 14,000 women screened during the 1966-67 mammography study and stored at Centralized Laboratory Services, Inc., an HIP affiliate. Other information will be developed from data already in the computer system. Presently coded and newly coded information will be related to blood sample information through computer analysis.

18. CLINICAL DIAGNOSIS OF BREAST CANCER BY XERORADIOGRAPHY

Higashi, Y., Saitama Cancer Center, Breast Surgery Clinic, *818 Komoro, Ina-Machi, Kitaadachi-Gun, Saitama-Ken 362, Japan*

In order to obtain more accurate diagnoses of breast cancer with less trouble, xeroradiography has been applied in the clinical diagnosis of breast cancer, along with mammography.

The pictures of xeroradiography are taken at the breast in two horizontal and sagittal directions, using the Xerox 125 system created by Fuji Xerox Co.

At present, breast carcinoma is correctly diagnosed 70% of the time by xeroradiography in comparison with 83% by mammography.

More correct clinical diagnosis of breast carcinoma will be brought about by improving exposure factors in xeroradiography.

19. TEST PHANTOMS FOR OPTIMIZING MAMMOGRAPHIC TECHNIQUE

Stanton, L., Hahnemann Medical College & Hospital, School of Medicine, Dept. of Radiation Therapy & Nuclear Medicine, *235 N. 15th St., Philadelphia, Pennsylvania,* 19102, United States of America

There is great need to both minimize patient exposure and maximize visibility of diagnostic details in mammography. A prerequisite to meeting this need is to measure average glandular exposure per view and detail visibility in the resulting roentgenogram. We have reported such data obtained using our present phantom, and now plan to improve its versatility.

OBJECTIVES: To develop and evaluate two breast phantoms. The first is a research unit, for comparing systems and optimizing technique. The second is a simple unit for routine quality assurance.

METHODS: 1. Visibility measurements will be improved by adding a 'detection yield' component, so one can estimate how well, as well as how small, an object is visible. This is especially important in detection of calcifications. 2. A study will be done to validate use of ionization chamber methods for depth dose measurements, to facilitate on-site evaluations. 3. Measurements with the research phantom will be done to optimize several mammography systems. The results can provide a preliminary estimate of their present capabilities and limitations. 4. The simple quality assurance phantom can help make image evaluation relatively routine, thereby assuring better mammographic technique in clinical studies.

20. X-RAY DIFFRACTION STUDY OF THE CHANGES IN DUCTAL STROMA IN BREAST CANCER AND THE DERMAL DEGENERATION CAUSED BY SOLAR EXPOSURE (ABBREV)

James, V. J., Halley, J. B., University of New South Wales, Dept. of Physics, *P.O. Box 1, Kensington, N.S.W. 2033, Australia*

OBJECTIVE: The determinative stromal changes which significantly antedate the epithelial proliferative process in carcinoma, especially those of the skin and breast, have been well documented. We propose to study normal and altered tissue by low angle X-ray techniques in order to elucidate the changes that occur on a molecular level.

APPROACH: An interpretation of the differences observed in the electron density profiles obtained from normal and altered tissue should reveal the changes in the molecular structure. Primarily the method could be used as a diagnostic tool for establishing the progressive alteration in molecular structuring.

21. TRIAL OF EARLY DETECTION OF BREAST CANCER

Chamberlain, J., Price, J., Joslin, C. A., Blamey, R. W., Forrest, A. P., Inst. of Cancer Research, Division of Epidemiology, *Clifton Ave., Sutton SM2 5PX, Surrey, England, United Kingdom*

This is an observational trial which aims to determine the effectiveness of alternative early detection programs in reducing mortality from breast cancer. Two populations of approximately 25,000 women aged 45-64 will be offered screening by clinical examination and mammography, two further populations of the same size and age distribution will be offered intensive education in breast self-examination, and at least four additional similar populations, serving as comparisons, will be offered no additional detection services over and above what is normally provided as good current practice. The field-work of the trial will continue for eight years and mortality from breast cancer will be measured in all populations for at least ten years.

22. FOLLOW-UP OF FLUOROSCOPICALLY EXAMINED TUBERCULOSIS PATIENTS IN RELATION TO CANCER INCIDENCE

Monson, R. R., Davis, F., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts,* 02115, United States of America

There is current interest in instituting mass screening programs of mammography to detect breast cancer in early stages. However, there is concern that the radiation used may itself have harmful side effects. In this study, the association between radiation received as a result of fluoroscopic examination during air-collapse therapy for tuberculosis and cancer is being assessed. The occurrence of other diseases both in relation to radiation and to isoniazid therapy will also be examined. This is a retrospective cohort study of approximately 9,000 women and men who were treated for tuberculosis in Massachusetts from 1930 onwards. These persons will be followed up from records and other sources. Rates of mortality and cancer morbidity will be compared internally, between radiated and non-radiated patients or between patients treated with and without isoniazid, and externally, with population mortality and cancer morbidity rates.

23. INVESTIGATION OF CHARGE TRANSFER ELECTRORADIOGRAPHY

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Electrophotographic methods, as applied to radiology (electroradiography), offer an opportunity for obtaining x-ray radiographs at substantially lower cost, lower dosages, and with rapid daylight development of the radiograph (within a few seconds), as compared with conventional silver halide x-ray film with intensifying screens. This has specific value for the mass screening of populations for mammography, cancer and other diagnostics. The objective of the present research is to continue to explore the applicability of charge transfer radiography (CTR), which offers certain fundamental advantages over the currently used Xerox and Xonics methods. While the current research has demonstrated that 9' x 14' radiographs of comparable quality and speed to xeroradiography can be obtained by CTR, there are strong indications that the speed can be increased substantially if trapping effects can be reduced by a compensating dopant in the tetragonal lead oxide x-ray photoconductor used. Furthermore, the scope for finding other photoconductors with the necessary properties appears much larger than originally anticipated.

24. NONINVASIVE SENSING OF SUBCUTANEOUS TEMPERATURES

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This work will continue evaluation of the potential of microwave radiometry for diagnosis of breast cancer and other medical problems having a thermal signature. In the coming year we will compare the performance of radiometers operating at 1 and 6 GHz in their ability to detect breast cancer. Comparison will be made with the same set of patients. We will begin new clinical studies involving attempts to detect deep venous thrombosis and abdominal infections. Laboratory work will involve attempts to develop antennas of improved resolution, and to develop a reliable antenna scanner.

BIBLIOGRAPHIC REFERENCES: A.H. Barrett, P.C. Myers, and N.L. Sadowsky, Microwave Thermography: Application to the Detection of Breast Cancer, pp. 375-385, Prevention and Detection of Cancer, Part II, Detection, edited by Herbert E. Nieburgs, Marcel Dekker Inc., New York, N.Y. 1978.

25. RADIOGRAPHIC IMAGING FOR CANCER DIAGNOSIS

Doi, K., Fennessy, J. J., Mullan, J. F., Skaggs, L. S., Collins, P. A., Metz, C. E., Duda, E. E., Frank, P. H., University of Chicago, School of Medicine, Dept. of Radiology, *5801 S. Ellis Ave., Chicago, Illinois,* 60637, United States of America

The aim of our research is to improve the diagnostic quality of radiographic images for cancer diagnosis and to minimize the patient exposure incurred during the radiographic examina-

tion. Our plan includes: 1) Application of magnification radiography with an ultra-high speed rare-earth recording system to chest radiography for early detection of pulmonary metastases, and lymphography for staging of malignant tumors; 2) in bone radiography, development of a high speed and high resolution technique for skeletal surveys to identify bone metastases and to assess disease progression; 3) in mammography, development of low dose imaging techniques to detect early breast carcinoma; and 4) evaluation of new stereoscopic techniques for accurate diagnosis of brain tumors. Clinical results based on blind studies or side-by-side comparison of radiographs will be analyzed by a group of radiologists in order to establish statistically the usefulness of the new techniques applied to various examinations.

The technical approach to applied and clinical studies of radiographic imaging described above is based on the application of methods of optical communication theory to the analysis of factors affecting detail visibility of radiographic images. This involves: 1) X-ray energy spectral analysis to study the relationship between the beam quality, patient exposure and image quality; 2) sensitometric evaluation of recording systems; 3) evaluation of modulation transfer functions to provide transfer characteristics of recording systems and of geometric unsharpness; 4) investigation of radiographic mottle to determine the effect of noise on detail visibilities of low contrast radiologic objects; and 5) computer simulation studies to optimize the physical parameters discussed above.

26. POTENTIAL TUMOR OR ORGAN IMAGING AGENTS

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Since its inception in 1965, this project has been involved in the synthesis and evaluation of potential radiodiagnostics. The synthetic program has been based on two approaches: 1) Pharmacological approach - labelling of drugs which have been reported to have or would be expected to have a predilection for a particular organ or tumor, and 2) biochemical approach - labelling of naturally occurring compounds or their precursors which are known to be biosynthesized and/or stored in certain organs or tumors.

In our design of organ or tumor imaging agents we will continue to focus much of our attention on diseases of the endocrine system. To achieve our goal, the chemical effort will deal primarily with steroids and amine derivatives and their radiolabelled counterparts. In general, compounds will be radiolabelled with gamma-emitting nuclides such as 125I, 131I, 82Br, and 18F. Once the synthesis of the radiolabelled compound has been achieved tissue distribution studies will be performed in normal or tumored animals (usually mice and rats). Those agents displaying selective localization in a target organ or tumor will then be studied in larger animals (usually dogs). Although current research emphasizes the development of imaging agents for tumors associated with adrenal, prostate, ovary, pituitary, and mammary gland, agents which display a potential for photoscanning other organs or tumors will not be ignored.

BIBLIOGRAPHIC REFERENCES: Counsell, R.E., Klausmeier, W.H., Skinner, R.W.S., Pozderac, R.V., and Weinhold, P.A. Synthesis of Radiobrominated Androgens, J. Labelled Cpds. and Radiopharm., 16, 165 (1979). Nordblom, G.D., Floyd, E.E., Schappa, L.W., and Counsell, R.E. Comparison of Cholesteryl Oleate and 19-Iodocholesteryl Oleate as Substrates for Adrenal Cholesterol Esterase, The Pharmacologist, 21, No. 3, 1979.

27. ANALOGUES OF 'BREAST SCANNING AGENTS'

Hosain, F., University of Connecticut, Health Center, School of Medicine, Dept. of Nuclear Medicine, *Farmington Ave., Farmington, Connecticut*, 06032, United States of America

This is part of a broader project. A summary of this subproject is not available.

28. NEW FLUORESCENT X-RAY TUBES FOR MAMMOGRAPHY

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Fluorescent radiation from Mo anode tubes is commonly used for film mammography. The quasimonoenergetic radiation at low energy (17-20 KeV) produces good subject contrast. However this low energy radiation does not penetrate well so it produces a high dose. Recent results have indicated that radiation of slightly higher energy (20-20 KeV) might provide adequate contrast, thus permitting imaging at much lower dose.

This study will investigate the fabrication of several 'transmolybdenum' (i.e., Z greater than ZMo) anodes for use in mammography. A demountable x-ray tube has been fabricated which will permit the interchange of several different anode materials. Rhodium and palladium anodes have been constructed by depositing thin film on graphite and copper substrates. Other anodes will be studied. A Si(Li) spectrometer interfaced to a minicomputer will be used to analyze the spectral distribution. Techniques can be adjusted to provide beams of similar spectral purity from the different anodes. This will permit a study of the effect of energy on subject and radiographic contrast.

Thermal loading presents the major problem in these new anodes. The data gathered from the work above should indicate which energies are most promising for mammography. Solutions for the specific elements will be sought. Thermal aging of the demountable anodes can be studied microscopically. Since the anodes can be easily replaced, destructive testing can also be done to determine operating limits. The final goal is to produce a new fluorescent anode tube for mammography with clinically useful output.

29. RADIOHALOGENATED NUCLEOSIDES FOR USE IN DIAGNOSTIC ONCOLOGY

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OBJECTIVE: To design and synthesize radiohalogenated nucleosides which would be of value in allowing a physician to monitor the progress (success or failure) of a therapeutic regimen. These agents are not intended initiallly to be useful in localizing cancerous tissue, although some may indeed prove useful for lung and breast tumors.

APPROACH: The program involves the synthesis and testing of a number of 18F- and 82Br-labelled compounds which may be active at the level of DNA synthesis. Specific compounds include 18F-5-F-2'-deoxyuridine (18F-5-FUdR), 18F-2'-F-2''-deoxyuridine (18F-2'-F-2'-UdR) 82Br-2'-Br-2'-deoxyuridine (82Br-2'-Br-2'-UdR) and 82Br-6-Br-uracil. Animal models employed are tumor bearing mice (Lewis lung carcinoma and Ehrlich ascites carcinoma) and rats (Walker 256 and Walker 256 chlorambucil resistant). Testing of the radiohalogenated compounds involves tumor uptake studies, to determine the usefulness of this series of compounds for non-invasive diagnostic procedures in oncology.

PROGRESS: Rapid chemical syntheses of 5-FUdR, 2'-F2'-UdR have been developed. High pressure liquid chromatography (HPLC) is used to purify the products. The synthesis and evaluation of the radiohalogenated 18F and 82Br analogs are in progress.

30. IMAGING OF THE HUMAN BODY BY NUCLEAR MAGNETIC RESONANCE

Mallard, J. R., Hutchison, J. M., Foster, M., Edelstein, W., Ling, R., Medical Research Council, Dept. of Bio-Medical Physics & Bio-Engineering, *Aberdeen, Scotland, United Kingdom*

OBJECTIVE: To image transverse cross-sections anywhere in the human body, displaying simultaneously, but separately, water concentration (i.e., concentration of hydrogen proton spins) and the spin lattice relaxation time T1 of the proton spins. T1 is related to the closeness of the binding of the water to macromolecules such as proteins. Such images may display abnormalities of water level and water function due to pathology.

APPROACH AND PROGRESS: Using a resistive electromagnet, and a system of orthogonal pulsed magnetic fields, combined with pi and pi/2 pulses of radiofrequency (1.7 MHz) transverse section images made up of 40 lines per frame have been achieved on humans in 8 minute exposures. Measures to reduce heart beating movement artifacts are being introduced together with better systems of determining T1 images.

During the same period since 1973 a considerable biological program has shown the normal pattern of T1 distribution in animals, the range of T1 values for normal tissues being fivefold from 150 msec to 800 msec. Malignant tissues give longer T1

than the corresponding normal tissue and calculations show that this method of imaging may be particularly valuable for imaging breast tumors and secondary tumor deposits in the liver. The reaction of host tissue to an implant of Yoshida sarcoma in the rat also elevates the T1 value in tissuing surrounding the tumor implant. It is believed that the NMR imaging technique may be of great value im imaging pathology other than tumors, particularly that giving rise to abnormal fluid pools, inflammation and changed water characteristics.

31. BREAST CANCER MORTALITY CHANGES IN A SCREENED POPULATION

Thomas, B. A., Boulter, P., Price, J., Gibbs, N., Jarvis Breast Screening, *Stoughton Rd., Guildford, Surrey, England, United Kingdom*

In the Guildford Breast Screening Project, one the British Breast Cancer Screening Trials, some 25,000 women aged 45-65 are being invited to attend screening centers (fixed and mobile) for clinical examination of the breasts and mammography using the Medichrome low radiation dosage system. General practitioner age/sex registers are being used as the basis for the recruitment of all women in the age group. Personal and medical data, particularly obstetric, breast feeding, and hormonal histories, past breast problems and family histories of breast cancer are being obtained from each woman. These invitations will be repeated two-yearly from updated registers with clinical examination only, carried out by a specially trained nurse, undertaken in the intermediate years. The doctors carrying out the main screening examinations will also read the mammograms, which will be classified according to Wolfe's duct patterns with a view to the determination of mammographic high risk groups. Prevalent, incident and interval cancers will be studied and long-term follow-up undertaken. Mortality rates in this district will be compared with those in other trial and control districts.

32. NATURAL HISTORY OF POSTMENOPAUSAL BREAST CANCER

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Population screening for breast cancer (palpation, xeroradiography) of 20,000 women 50-64 years of age, at regular intervals (12-18 months) will enable the investigators to study factors which determine incidence and growth rates of preclinical breast cancer occurring after menopause. Particular attention will be paid to endocrine and nutritional factors. Urine is being collected for determination of 11-deoxy-17-ketosteroids and frozen for future research (prospective study). Body weight and height and skinfolds are being measured. Blood pressure is taken and data on antihypertensive drug treatment and other possible risk factors are being collected. Blood samples are being taken at the second examination.

33. STUDY OF VALIDITY OF CLINICAL EXAMINATION AND X-RAY MAMMOGRAPHY AS SCREENING TESTS FOR BREAST CANCER (ABBREV)

Chamberlain, J., Burn, J. I., Price, J., Nathan, B. E., Clifford, R. S., Simpson, P., University of London, University College Hospital Medical School, Dept. of Community Medicine, *University St., London WC1E 6JJ, England, United Kingdom*

The aim of this study is to determine the error rates of clinical examination and mammography in screening for breast cancer and to measure reproducibility between two observers performing the same test. Women over 40 years of age are screened in a well-women clinic where, in addition to a medical history, they have two independent examinations of the breasts, one by a nurse and one by a doctor, and mammography, using the low dose medichrome film system. Mammograms are read independently by two radiologists. Women in whom an abnormality is detected are referred for surgical assessment, when necessary biopsied, and in those in whom cancer is found, follow-up is continued for at least 15 years. To get some idea of the false negative results (the cancers which would be missed by annual re-examination), all women are asked to attend for re-screening at six month intervals for the first year and then to have one further re-examination two years after initial entry into the study; this, it is hoped, will help determine optimum screening frequency. To date about 6,000 screenings have been done in 2,000 women and 32 cancers found. The economic study is trying to assess both the costs and the benefits of screening. Not only are the health service costs of providing screening taken into account, but also all costs resulting from referral to hospital for surgical opinion and biopsy and costs of treating cancers found. These will be compared with conventional management of breast disease in a system without screening. Benefits are being assessed by trying to obtain a measure of the value which women themselves put on the screening service. It is hoped that eventually some measure of the effectiveness of screening in reducing mortality can also be included.

34. SCREENING FOR NEOPLASMS IN IRRADIATED POPULATIONS

Hempelmann, L. H., Woodard, E., Shore, R., Rogoff, R., University of Rochester, School of Medicine & Dentistry, Dept. of Radiology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

The summary for this project is under entry no. 13.

35. SCREENING FOR DETECTION OF BREAST CANCER

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The summary for this project is under entry no. 14.

36. DATA MANAGEMENT CENTER FOR BREAST CANCER DETECTION

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The summary for this project is under entry no. 15.

D. OTHER TECHNIQUES FOR DETECTION AND LOCALIZATION OF BREAST TUMORS

37. RISK OF MULTICENTRIC IN SITU, INVASIVE CARCINOMA AND AXILLARY NODE METASTASES WITH FOCAL DUCT CARCINOMA OF THE BREAST (ABBREV)

Lagios, M. D., Kempson, R. L., Margolin, F. R., Childrens Hospital of San Francisco, Dept. of Pathology, *3700 California St., Box 3805, San Francisco, California*, 94118, United States of America

Duct carcinoma in situ, a non-invasive form of breast cancer, has accounted for 20% of all new breast carcinomas accessioned at Children's Hospital of San Francisco (58 cases) to date. Most of these cancers are small xeromammographically identified lesions whose natural history and clinical significance are unknown. Current surgical therapy designed for large invasive cancers should be re-evaluated for focal duct carcinomas in situ which appear from our preliminary data to have no occult invasive component or axillary metastases when smaller than 25 mm.

The goals of this investigation will be to determine: 1) Whether localized duct carcinoma in situ is amenable to limited surgical intervention (tylectomy, quadrant excision, subcutaneous mastectomy) without risk of residual cancer in the breast. 2) Whether mammography can identify those patients with localized disease preoperatively and so facilitate patient management. 3) Whether patients with duct carcinoma in situ represent a recognizable high risk group separate from patients with breast cancer in general.

Mammograms will be reviewed independently to attempt measurement of the size and extent of disease within the breast. The mammographic preoperative estimate will be correlated with the results of a serial subgross and radiographic examination of the mastectomy specimen, the standard method used in our laboratory since July 1975 (Lagios, 1977).

The feasibility of predicting the extent of disease by mammographic findings in patients with subsequent biopsy proven focal duct carcinoma in situ (DCIS) smaller than 25 mm, will be compared to that in patients with other specified forms of breast cancer. The frequency of occult invasive and multicentric carcinoma within the breast resected for focal DCIS will be determined precisely by the serial technique, and the relative risks of such occult cancer will be established in patients with focal DCIS and compared to that of other specified forms of breast carcinoma.

38. ISOPROTEINS IN NORMAL AND MALIGNANT BREAST TISSUES

Balinsky, D., Iowa State University of Science & Technology, College of Humanities & Sciences, Dept. of Biochemistry & Biophysics, *Beardshear Hall, Ames, Iowa*, 50010, United States of America

OBJECTIVE: To detect, quantitate and characterize various isoenzymes or non-enzymic isoproteins in normal, benign and neoplastic breast tissue. These findings might help in the detection of breast cancer at an early stage, or of disseminated breast cancer following local treatment of the primary cancer.

39. IODINATED ESTROGENS IN BREAST CANCER

Caspi, E., Longcope, C., Arunachalam, T., Worcester Foundation for Experimental Biology Inc., *222 Maple Ave., Shrewsbury, Massachusetts*, 01545, United States of America

Procedures for nanogram level synthesis of 125I and 75Se selenoestradiol analogs were developed. The samples showed the same activity as material prepared in the macroscale synthesis. The evaluation of the utility of the prepared samples in competitive binding with estradiol receptors and, eventually, in early detection and therapy of breast tumors will be continued.

BIBLIOGRAPHIC REFERENCES: Iodoestrogens, Syntheses and Interaction with Uterine Receptors. Thangavel Arunachalam, Christopher Longcope and Eliahu Caspi. J. Biol. Chem., in press, 1979.

40. PROGRAM IN RADIONUCLIDE STUDIES OF TUMORS AND GROWTH

Spencer, R. P., Hosain, F., Sripada, P. K., Banerjee, S. N., Emran, A., University of Connecticut, Health Center, School of Medicine, Dept. of Nuclear Medicine, *Farmington Ave., Farmington, Connecticut*, 06032, United States of America

The study proposes to use conventional and newly developed radiopharmaceuticals to study both tumor growth and the response to medication. Results are checked against models evolved to describe these events. An active area of work is the elucidation of the necessary and sufficient conditions for various radiopharmaceuticals to exert an action or uptake in normal and neoplastic tissue. Thus, multiple analogues have been synthesized of bone imaging agents in order to determine the spatial and charge restrictions on their uptake. The effects of hormonal therapy are being studied on bone scans in men with prostatic carcinoma treated with diethylstilbestrol, and in women with metastatic breast carcinoma under therapy with tamoxifen. Synthesis of several new radiopharmaceuticals has been accomplished, in an effort to examine active sites of enzymes through the use of radiolabeled substrates or analogues.

41. LOW DOSE BREAST ELECTRON RADIOGRAPHY (IONOGRAPHY)

Shaber, G. S., Gorson, R. O., Lassen, M., Edeiken, J., Thomas Jefferson University, Jefferson Medical College, Dept. of Radiology, *1025 Walnut St., Philadelphia, Pennsylvania*, 19107, United States of America

The object of this research is to improve the imaging characteristics for high frequency objects (calcific specks) of an electron radiographic chamber by reduction of scatter radiation through the incorporation of a moving slit grid and utilization of magnification techniques. In addition, the effect on detectability of high frequency objects by image polarity reversal and varying amounts of edge enhancement will be studied. Evaluation of the improvement in imaging characteristics of the modified electron radiomammography imaging chamber for high contrast objects will be determined by: 1. Resolution through measurement of its edge spread function (ESF) and line pair resolution of a gold test pattern. 2. Definition through generation of receiver operating characteristic curves (ROC) and imaging of a modified Stanton mammography phantom. 3. Cancer detection through comparison with conventional techniques (film and xeroradiography) of electron mammographic radiographs of suspected neoplastic breast lesions. 4. Sensitivity through measurement using film and thermoluminescent dosimeters of the dose necessary to obtain optimally imaged abnormal breasts.

42. DEVELOPMENT OF TUMOR AND ORGAN IMAGING AGENTS

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This proposal deals with the design and preparation of agents potentially useful for visualization of tumors of steroid target organs such as the adrenal, prostate, and mammary glands, and for the diagnosis and study of diseases which may affect the adrenal gland. The kinetics of the distribution of the proposed agents will be studied in experimental animals. Thin-layer chromatography, high pressure liquid chromatography, and nuclear magnetic resonance spectroscopy will be used to purify, identify, and quantitate the proposed agents. The proposed agents will be synthesized to contain 18F. The kinetics of their distribution and potential as radiopharmaceuticals for visualization of the steroid target organs will be evaluated.

43. SYNTHESIS OF NEW 75SE ORGAN SPECIFIC IMAGING AGENTS

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The objectives of the proposed research are the synthesis and biologic evaluation of imaging agents for the detection and differential diagnosis of disorders, including carcinoma, of the pancreas, adrenals, breast and brain. Successful treatment of these disorders depends upon early detection; however, this is seldom achieved by scintigraphic imaging techniques because of shortcomings associated with the radiopharmaceutical. The development of new organic radiodiagnostic agents which possess greater organ or disease selectivity will provide more informative scintigraphic images, thus enabling the early detection of the suspected pathophysiology and improving the prognosis of the patient.

Our recent experience in selenium chemistry has indicated that the approach with the highest probability of success involves the preparation of analogs of the appropriate organ or disease selective drugs in which the selenium is either disubstituted or located in an aromatic ring. This will provide for greater isoelectronic and isosteric analogy to the parent drug and for greater stability to metabolic degradation. We propose that selenium containing analogs of the following classes of compounds be prepared and evaluated as potential imaging agents: aromatic amino acids for the pancreas, adrenal corticosteroid enzyme inhibitors for the adrenal, estradiol for breast cancer, levamisole for the immune system, and CNS active drugs for the brain.

The prepared substances will be evaluated in animals to determine their pharmacokinetics, biologic distribution, toxicity and ultimate fate. The stability of these agents will be investigated by double labeling (14C or 3H and 75Se). Any radiopharmaceutical emerging from this work which exhibits potential for effective imaging in man will be considered for evaluation in a clinical trial.

BIBLIOGRAPHIC REFERENCES: A semi-micro synthesis of selenophene. Paula M. Jacobs, Michael A. Davis, Harriet Norton. J. Heterocyclic Chem. 14:1115; 1977.

44. SCANNING ACOUSTIC MICROPROBE FOR CANCER DIAGNOSIS

Barber, F. E., Sonnenfeld, M., Sletzinger, L., Harvard University, Boston Campus, School of Medicine, Dept. of Radiology, *25 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The summary for this project is under entry no. 12.

45. TRIAL OF EARLY DETECTION OF BREAST CANCER

Chamberlain, J., Price, J., Joslin, C. A., Blamey, R. W., Forrest, A. P., Inst. of Cancer Research, Division of Epidemiology, *Clifton Ave., Sutton SM2 5PX, Surrey, England, United Kingdom*

The summary for this project is under entry no. 21.

46. THE EFFICACY OF BREAST SELF-EXAMINATION

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Although breast self-examination intuitively seems to be a feasible procedure for laymen once they have been educated in how to do it and have experience in the procedure, there are no data suggesting that this is indeed the case. Therefore, we are carrying out an evaluational study. We hypothesize that women who have at frequent intervals practiced breast self-examination, will find their breast cancer lesions at an earlier stage than those who have not adopted the procedure. Thus, we would hypothesize that in a service treating breast cancer a greater proportion of women with early lesions would have in the past frequently practiced breast self-examination than is the case with women with lesions which have progressed to a later stage. With Dr. Takuma Nemoto, Associate Chief Breast Cancer Surgeon at Roswell Park Memorial Institute, we have devised a data-collection procedure which consists of the participants filling out a 1-page questionnaire. To date, 168 such questionnaires have been filled out. Data collection will continue over the next year.

47. BREAST CANCER DETECTION BY BREAST SELF-EXAMINATION

Foster, R. S., Worden, J. K., Costanza, M. C., Lang, A. P., University of Vermont & State Agricultural College, School of Medicine, Dept. of Surgery, *85 S. Prospect St., Burlington, Vermont,* 05401, United States of America

We propose studies to obtain data to confirm or refute the hypotheses: 1. That breast self-examinaton can lead to earlier breast cancer detection and decreased breast cancer mortality, and 2. that public health education programs can significantly increase the frequency and quality of breast self-examination in a population of women.

We plan to extend our previous findings which suggested a relationship between increased frequency of breast self-examination performance and more favorable clinical and pathologic stages of breast cancer. This will be done by determining the relationship between breast self-examination performance and breast cancer mortality. Studies are planned to determine the effect of public education on the frequency and quality of breast self-examination performance. A public health education program on breast cancer and breast self-examination was conducted in the State of Vermont during the years 1974-1978 and it is our intention to determine the effect of that program on both the clinical and pathologic stages of breast cancer in Vermont women in the years 1979 through 1984.

48. WOMEN'S ACCEPTANCE OF BREAST SELF-EXAMINATION

Kegeles, S. S., Grady, K., Lund, A. K., Willms, J., University of Connecticut, Health Center, School of Dental Medicine, Depts. of Behavioral Sciences & Community Health/Psychology, *Farmington Ave., Farmington, Connecticut,* 06032, United States of America

The proposed research is directed toward the development of cost-effective, feasible methods for the encouragement of regular, monthly breast self-examination by a majority of women. Breast self-examination, as a technique of breast cancer detection is a technology which needs definition, measurement, and transference to the population of women who should be practicing it. Using a behavioral analysis of the compliance problem of BSE as a theoretical framework, the research specifically proposes to test two kinds of compliance-enhancing techniques in two separate studies of six months each with three-month and one-year follow-ups. Stimulus control techniques involve action instructions, calendar recording, and post card reminders. Reinforcement control techniques involve material extrinsic reward (lottery ticket), social extrinsic reward (letter of appreciation), and training in self-management techniques. Frequency of performance, accuracy of performance, and medical evaluations sought are the major dependent variables. Independent variables include the experimental techniques as well as a number of background characteristics of the women. The overall goal is the development of a variety of compliance-enhancing techniques, for each of which probable effectiveness and potential utility can be specified.

II. CLINICAL LABORATORY PROCEDURES FOR DIAGNOSIS AND PROGNOSIS OF BREAST CANCER IN MODELS AND HUMANS

A. HORMONE RECEPTOR DETERMINATIONS IN DIAGNOSIS AND PROGNOSIS

49. HORMONE RECEPTORS AND ACTION IN HUMAN BREAST CANCER

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OBJECTIVE: To predict the response to endocrine ablation or additive hormone therapy with greater accuracy in advanced breast cancer.

APPROACH: The hormone receptor profile for a number of steroid hormones is determined in primary and metastatic breast cancer. Methods for the characterization and quantitative measurement of estradiol, cortisol, dexamethasone and progesterone receptors are routinely used. In addition the nuclear binding of estradiol is studied. The presence or absence of these receptors is correlated to responses to endocrine treatments.

PROGRESS: Estradiol receptors were detected in 50% of 650 cases in significant amounts, in the cytosol of the tumors. Nuclear binding was found in 75% of these cases; the remainder were without detectable translocation of estradiol. Glucocorticoid receptors were found in 23% of all cases, while a transcortin-like cortisol binding protein was detected in over 95% of all cases studied. Approximately one-third of cases showed progesterone binding activity. Studies indicate that some tumors have receptors for a number of steroid hormones indicative of multiple hormone dependency. A significant proportion of ER positive tumors show no nuclear binding.

50. ESTROGEN-RECEPTOR ASSAY IN THE MANAGEMENT OF BREAST CANCER

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This is part of a broader project. A summary of this subproject is not available.

51. PROLACTIN RECEPTOR CONCENTRATIONS IN BREAST CANCER

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Prolactin markedly influences many aspects of normal breast physiology which are similar to events associated with growth. In the study of women with cancer of the breast it would therefore seem relevant to quantitate the concentration of prolactin receptors in the breast tumor tissue. In order to measure breast prolactin receptor levels, we plan to develop a radioimmunoassay for solubilized prolactin receptor. The influence of circulating hormonal levels, including estrogens (E1, E2, E3), progesterone, testosterone, cortisol, and prolactin, on prolactin receptor level in malignant breast tissue will then be investigated and correlated with the patient's clinical course.

52. MAMMARY CANCER AND THE NUCLEAR ESTRADIOL RECEPTOR

Frankel, F. R., Senior, M. B., Sun, L., University of Pennsylvania, School of Medicine, Dept. of Microbiology, *36th & Hamilton Walk, Philadelphia, Pennsylvania,* 19174, United States of America

Steroid receptor proteins appear to be regulatory molecules that interact with the cell's genetic material to control gene expression. Some human mammary tumors contain significant amounts of the estradiol receptor, and these tumors often respond to various endocrine therapies with remission of tumor growth. We wish to know more about the nature of the nuclear form of the receptor protein and more particularly, what kind of interaction it shows with chromatin and how hormone analogues may affect this interaction. We have shown that when

estradiol is administered to isolated rat uteri or MCF-7 cells, a line of human mammary tumors cells, it binds to chromatin. This estradiol is preferentially released from the chromatin by ingestion with various nucleases with the concomitant production of hormone-bound nucleosomes and hormone-receptor complex bound to a fragment of DNA. Transcriptionally active fractions of chromatin are enriched in estradiol. We now wish to determine (1) whether nucelosomes containing estradiol otherwise differ from the bulk nucleosomes, i.e., whether we can detect the presence of special 'acceptor' proteins or unique DNA sequences; (2) whether the components of active chromatin are different from those of the bulk chromatin; (3) whether steroid receptors occur in patches or singly along the chromatin; (4) whether antiestrogens show similar binding to chromatin, or alter the binding of estradiol; and (5) whether different clones, or mutants of MCF-7 cells show different responses to steroid treatment and, if so, whether the interaction of their receptors with chromatin will differ from that occurring in wild type cells.

BIBLIOGRAPHIC REFERENCES: Enrichment of estradiol-receptor complexes in a transcriptionally active fraction of chromatin from MCF-7 cells. Richard W. Scott and Fred R. Frankel, Proc. Natl. Acad. Sci. USA 77: 0000 (1980), in press.

53. ENDOCRINE TUMORS - STEROID RECEPTORS AND THERAPY

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The overall goals of this proposal are to study the levels and regulation of steroid receptors in endocrine-responsive tumors and thus to improve the therapy of these tumors with steroids, to develop and advance the use of antisteroids, and to evaluate treatments that might prevent muscle wasting that occurs in the tumor-bearing host. The specific objectives are: (1) to relate the response to therapy with steroids to the endogenous and regulated levels of steroid receptors in estrogen-dependent and -independent mammary tumors; (2) to initiate steroid receptor studies and therapeutic trials with the transplantable androgen-dependent rat tumor R-3327; (3) to stimulate the development of antisteroids for use in the treatment of endocrine-responsive tumors; (4) to correlate chemical structure and biological activity of steroid analogues, with particular emphasis on analogues of progesterone and other progestins; (5) to study the basis for resistance of lymphoid tumors to glucocorticoids and other endocrine tumors to steroid therapy; and (6) to explore the possibility that androgen or progesterone analogues, by competing with glucocorticoids for receptors in muscle, can alleviate muscle wasting in advanced cancer.

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54. THE ROLE OF OESTROGEN RECEPTORS IN ADJUVANT ENDOCRINE THERAPY FOR EARLY CANCER OF THE BREAST

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OBJECTIVE: To determine whether the assay for oestradiol receptor (E2R) in breast cancer at the time of mastectomy will help rationalize the use of adjuvent systemic therapy.

APPROACH: It is widely accepted that the outcome of treatment for early breast cancer is predetermined by the extent of micrometastases at the time of diagnosis. Early results of trials of adjuvent chemotherapy have demonstrated promising results only in premenopausal women with positive nodes. It has therefore been suggested that benefit is mediated via an endocrine pathway. A prospective trial has been established to evaluate the antioestrogen Tamoxifen as systemic therapy following mastectomy for both premenopausal and postmenopausal women with early breast cancer. In parallel with this trial, samples of the primary tumor will be assayed for E2R. The results of these tests will not influence treatment but eventually it will be possible to determine whether the sub-group of women with E2R positive tumors are the only ones to benefit from adjuvant endocrine therapy and whether the E2R negative tumors demand a chemotherapeutic approach.

55. STUDIES ON THE ROLE OF ESTROGEN RECEPTORS IN PREDICTING SUBSEQUENT THERAPY FOR RECURRENT BREAST CANCER

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OBJECTIVE: Endocrine ablation such as hypophysectomy, adrenalectomy or oophorectomy is the therapy of choice in recurrent breast cancer. It has been demonstrated recently that clinical response to hormone therapy is correlated with the presence of estrogen receptors (ER) in tumor tissue. Therefore, measurement of ER in patients with recurrent breast cancer has been performed, as this is a very valuable factor in weighing indications for endocrine ablation.

APPROACH: Samples are obtained from the patients admitted to the Saitama Cancer Center. Biopsies were performed in the operating room at the beginning of radical mastectomy. The dextran-charcoal method originally described by Korenman has been used for specific quantitative estrogen receptor assays.

PROGRESS: The basic goal of this study is to evaluate the clinical correlation of ER and endocrine responsiveness. As the Saitama Cancer Center just opened in November 1975, we shall report the results of this study in a few years.

56. STUDIES ON ESTRADIOL AND PROGESTERONE RECEPTORS IN MALIGNANT TUMORS WITH SPECIAL REFERENCE TO BREAST CANCER (ABBREV)

Norgren, A., University Hospital of Lund, Depts. of Lung Medicine/Research, *E. Blocket, S22185 Lund, Sweden*

OBJECTIVES: 1) Thorough testing of currently used methods in receptor research with the aim to improve, for instance, yield of receptor, and to make possible the estimation of total concentration of cytosol receptor protein. 2) Elaboration of experimental biological test systems for the study of control mechanisms for receptor synthesis. 3) Study of importance of the different receptor profiles in prospective clinical breast cancer trials with regard to prognosis of the disease and the effect of adjuvant therapy. 4) Estimation of hormone receptor levels in hormone dependent malignant tumors other than breast cancer.

57. ESTROGEN RECEPTOR (ER) IN NORMAL AND TUMOR TISSUE OF THE BREAST - CORRELATION WITH CLINICAL AND PARACLINICAL PARAMETERS

Rivadeneyra, J. H., Gomez, C. P., GuzmanPatraca, C., Rabago, M., Instituto Mexicano del Seguro Social, Dept. of Pathology, *Av. Cuauhtemoc No. 330, c/o Hospital de Oncologia - Centro Medico Nacional del IMSS, Mexico City 7, Distrito Fed., Mexico*

The results are presented in the following order: type of tumor, number of tumors of a given type, percentage of ER positive tumors, mean value expressed as fm/mg/cp: Malignant tumors: not otherwise specified - 65, 72, 93.19; medullary - 11, 45, 52.80; tubular - 2, 100, 52.00; lobular - 5, 40, 58.00; and c. phyllodes - 3, 100, 22.67. Benign tumors and diseases: fibroadenoma -16, 38, 43.80; cystic mastopathy - 5, 60, 51.70; c. phyllodes - 3, 67, 110.50.

58. COMPARATIVE STUDY OF ESTROGEN RECEPTOR ACTIVITY IN MAMMARY CANCER BY RADIORECEPTOR ASSAY AND FLUORESCENCE MICROSCOPY

Remmele, W., Frank, K., Heine, M., Heicke, B., Municipal Hospital, Dept. of Pathology, *Schwalbacher Str. 62, D6200 Wiesbaden, Federal Republic of Germany*

OBJECTIVE AND APPROACH: The purpose of the project is to compare the results of estimation of steroid receptor activity by radioreceptor-assay (Prof. Heicke, Univ. of Mainz-Bioscientia Ingelheim) and by the fluorescence microscopy method of Lee (Amer. J. Clin. Path. 70: 197-203, 1978). The method of Lee is used as originally described as well as in a modified way developed in our laboratory.

PROGESS: Series of experiments has just started; no data are yet available.

59. STUDIES ON ANOMALOUS RECEPTORS IN BREAST CANCER

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Recent research in this laboratory has described two anomalous nuclear estrogen binding macromolecules in human breast cancer. These two entities are 1) the uncharged (unoccupied) nuclear estrogen receptor and 2) the nuclear Type II estrogen binding sites. Information about these two anomalous nuclear receptors may provide insight into the regulatory processes of human breast cancer. More immediately, information about these two anomalous nuclear receptors will be required to develop specific and accurate assays of charged (occupied) nuclear estrogen receptors. Such assays for charged nuclear estrogen receptors, alone or in concert with present techniques, promise significant improvements in the degree of accuracy of the predictions of response to endocrine manipulation in patients with metastatic breast cancer.

Human breast cancer tissue will be pooled (according to rigid histologic and biochemical criteria) and used as the experimental tissue for this study. The affinity of uncharged nuclear estrogen receptor (ER) for the chromatin will be contrasted with the affinity of the charged nuclear ER. Using a competitive displacement assay, we will determine if charged and uncharged nuclear ERs bind to the same nuclear acceptor site. The nuclear Type II estrogen binding sites will be biochemically characterized. The estrogen binding characteristics will also be determined. Using anti-ER antiserum (provided by Dr. E. V. Jensen), the cross-reactivity of the nuclear Type II EBS for the anti-ER antiserum will be determined. The information obtained will be used to design an accurate and valid assay for the charged nuclear ER.

60. ROLE OF ESTROGEN AND OTHER HORMONES IN BREAST CANCER

Butler, W. B., Kelsey, W., Goran, N., Michigan Cancer Foundation, Dept. of Chemistry, *110 E. Warren St., Detroit, Michigan,* 48201, United States of America

Many human breast tumors contain estrogen receptors and many that do are responsive to hormone therapy. The growth of cells from estrogen dependent human and animal tumors in vitro, however, is not estrogen dependent nor, in most cases, estrogen responsive. We propose to test the hypothesis that the role of estrogen in breast cancer is to act not as a mitogen, but rather to induce in the cells properties essential or related to the malignant state, including not only tumor growth but also invasion and metastasis. We will use the human breast cancer cell line MCF-7 as a model system for these studies. MCF-7 requires estrogen in order to form tumors in nude mice but is not dependent on estrogen for growth in culture. We have shown that estrogen at physiological concentrations stimulates the production of plasminogen activator by MCF-7 cells under conditions where the growth rate is unaffected by estrogen. We have clones of MCF-7 which differ in morphology, resistance to the antiestrogen tamoxifen and ability to produce plasminogen activator. We propose to study the effect of hormones, including estrogen, progesterone, insulin and prolactin, on the properties of these clones in vitro. We will measure properties which have been considered as possible markers of transformed cells, including: Colony formation in soft agar, reactivity to concanavalin A, production of plasminogen activator, morphology and growth pattern in collagen-coated sponge cultures. We will also measure resistance to the antiestrogen tamoxifen and the levels of estrogen and progesterone receptors and will test the effect of hormones on these clones in an in vitro assay for tumor cell invasion. The in vitro results will be correlated with the need of the clones for estrogen and their ability to form tumors, invade and metastasize in nude mice. In this way, we will attempt to define those cell properties related to tumor formation by breast cancer cells and the role of hormones, especially estrogen, in the process.

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61. STEROID RECEPTORS AND INDUCIBLE PROTEINS IN BREAST TUMORS

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OBJECTIVE: The aim of this project is to determine if estradiol inducible proteins are better markers for hormone dependent breast cancer than the estradiol receptor alone.

APPROACH: Estradiol receptors and the estradiol inducible protein (peroxidase and progesterone) receptors are being measured in both normal animal tissues and breast tumors. The correlation between the presence of these parameters in human breast cancers and response to endocrine therapy is being investigated. It is hoped to determine if the presence of the inducible proteins adds to the predictive ability of the estradiol receptor.

62. STEROID HORMONE RECEPTOR CONTENT AND PREDICTIVE TEST FOR CHEMOTHERAPY OF BREAST CANCER

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OBJECTIVES: a) Information on biochemically prognostic factors relevant to selection of patients for adjuvant postoperative therapy regimens. b) Planning of individual hormonal and/ or cytotoxic chemotherapy in breast cancer.

APPROACH: Hormone receptor assay (17-beta estradiol (ER), progesterone (R 5020) (PgR)-receptor): Receptor determination is done by the dextran charcoal adsorption technique (according to EORCT, 1973). Definition of receptor content (fmol/mg cytosol protein): ER (PgR)-negative: less than 5 (less than 20), -poor: 5-10 (20-50), -rich: greater than 10 (greater than 50).

In vitro chemoresistance test: Native, mechanically isolated tumor cell suspensions were tested for a common primary chemoresistance, using a simple standardized in vitro test system without trypsinizing procedures. Therefore the effect of adriamycin (ADM; 10 to the 4th power - 10 to the minus first power mg/ml) as a non-cycle specific compound will be studied on the 3H-uridine (UdR) incorporation in trichloracid precipitable cell material. Definition of chemoresistance: reduction of UdR-incorporation by ADM (10 to the minus 2nd power mg/ml) less than 25% compared with control values.

PROGRESS: Tissue of primary untreated breast cancer of different histology and tumor stage without distinct metastases was investigated in 53 patients (13 pre-, 40 postmenopausal): ER (PgR)-negative - 36% (54%), ER (PgR)-poor - 11% (20%), and ER (PgR)-rich - 53% (26%). There were more receptor-rich cases in postmenopausal, as compared to premenopausal, women. Out of a total number of 19 ER-negative cases 8 (42%) were chemoresistant (PgR: 10/19 equals 53%) in comparison to 24/28 equals 86% of the ER-rich cases (PgR: 8/9).

Lack of ER- and/or PgR-receptors in primary breast cancer tissue is associated in vitro with increased response to cytotoxic drugs.

63. CYTOCHEMICAL STUDIES ON HORMONAL RECEPTORS IN BREAST CANCER

Tremblay, G., Shyamala, G., Buell, R. H., McGill University, Inst. of Pathology, Dept. of Pathology, *3775 University St., Montreal, Quebec,* H3A 2B4, Canada

OBJECTIVE: Biochemical assays of mammary carcinoma tissue for estrogen receptor (ER) provide quantitative data allowing for the prediction of patient response to hormonal therapy but provide little information on the distribution of ER and fail to predict the observed clinical response in about one-third of patients. Recently, cytochemical techniques were developed demonstrating a heterogeneous population of ER positive and negative tumor cells within many mammary carcinomas. This cellular diversity, not evident in biochemical assays, suggests a partial explanation for unexpected therapeutic failures. The object of this project is to develop techniques which will permit the differentiation on tissue sections of ER positive and negative cells in human mammary carcinomas. Special emphasis will be placed on the distribution of ER in atypical (pre-cancerous) lesions and the various histologic patterns of primary breast

carcinoma. The long range plan of the project is a correlation of the cytochemical studies, biochemical assays and the biologic evolution of the carcinoma.

APPROACH: To identify ER positive and negative cells in tissue sections, dry-mount or thaw-mount autoradiography and a peroxidase/anti-peroxidase immunocytochemical technique will be used. The accuracy of the methods will first be verified by studying the distribution of ER in the uterus of BALB/c mice after in vitro incubation with or without specific inhibitors and comparing this with known results obtained from in vivo injection of 3H-estradiol. Once characterized, the methods will be applied to a study of human mammary carcinoma.

PROGRESS: The techniques of dry-mount and thaw-mount autoradiography have been successfully used to demonstrate ER positive cells in the uteri of BALB/c mice after in vivo injection of 3H-estradiol. In vitro incubation schemes are being tested which yield results comparing favorably with those observed after in vivo injections. Preliminary results from the incubation of several human breast cancers have also been obtained. For the immunocytochemical technique, the antigen 17-beta-estradiol-6-(O-carboxymethyl) oxime-bovine serum albumin has been synthesized and used for immunization of rabbits. The antisera obtained are being tested for titre and cross-reactivities. In addition, experiments are being done to localize ER in tissue previously studied by autoradiography.

64. RECEPTOR STUDIES IN HUMAN BREAST CANCER

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We have demonstrated that estradiol receptor from two lines of rat mammary tumor MTW9 differ by chromatographic, kinetic and DNA binding properties. MTW9-MtT does not regress after ovariectomy, MTW9-P does regress. MTW9-MtT, the rat mammary tumor grown by coimplantation of the mammosomatotropic tumor MtTW10, shows ovariectomy-induced regression when MtT is resected. MTW9-MtT tumor cytosol receptor shows much less binding to DNA than does receptor from MTW9-P; after resection of MtT, DNA binding is similar. These data suggest that the differences between tumor receptors observed in our animal model may allow differentiation between tumors which have estradiol receptor and either regress or fail to regress after ovariectomy.

We propose to study human breast cancers which contain estradiol receptor by the techniques described which differentiate responsive from non-responsive tumors. Differences in receptor behavior would then be correlated with response to endocrine treatment. If such a study of estradiol receptors in mammary cancer would identify hormone-responsive tumors, current therapy would be improved.

65. ROLE OF PROLACTIN RECEPTORS IN HUMAN BREAST CANCER

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The research proposed in this project is directed towards understanding the possible role of prolactin and prolactin receptors in human breast cancer. Preliminary studies by the applicant show that seventy-five percent of the tumors have greater than 2.5 fmoles/mg protein of prolactin receptors; twenty percent of these tumors have prolactin receptors but no estrogen receptors. These data suggest that in at least some tumors, estrogen may not be important for tumor growth. Serum estrogen and prolactin will be measured by radioimmunoassay; prolactin receptors will be measured using 125-I-iodo human prolactin on partially purified membranes from breast tumors, non-malignant breast tissue and normal breast tissue; estrogen receptors will be measured on tumor cytosols. The clinical responses to endocrine ablative procedures of patients whose tumors have both estrogen and prolactin receptors as opposed to only one receptor will be compared. The prolactin receptor concentrations of malignant vs. non-malignant tissue from the same patient will also be compared. Prolactin receptors from normal, non-malignant and malignant breast tissues will be characterized in terms of binding kinetics and hydrodynamic properties.

66. A STUDY OF HORMONE RECEPTORS IN TUMOR TISSUE

Skinner, L. G., Barnes, D. M., Lloyd, E. J., Ribeiro, G. G., Bush, H., Paterson Lab., Dept. of Clinical Research, *550 Wilmslow Rd., Manchester M20 9BX, England, United Kingdom*

OBJECTIVES: (1) To increase the value of receptor assay in predicting hormone responsiveness of breast tumor by improvement and simplification of our present methods for estimating cytoplasmic oestradiol and progesterone receptors and nuclear oestrogen receptors, and to extend the scope of receptor analysis by inclusion of additional hormone receptors. (2) To continue and extend clinical pilot studies on breast carcinoma to provide information on: (a) receptor status and correlation with hormone therapy, (b) relationship between receptor status and response to cytotoxic chemotherapy, (c) usefulness of receptor profile of primary tumor as a predictor of hormone responsiveness of subsequent metastases, (d) effects of chemotherapy, radiation, hormone and anti-oestrogen treatment on receptor site status, and (e) relationship between receptor status and stage of disease.

APPROACH: Current methods of assaying receptors in general are hampered by inavailability of sufficient tissue on many occasions. An attempt will be made to develop more sensitive methods for the assay of receptor sites based on the availability of specific antibody to the receptor protein: These would include use of fluorescently labelled antibody in tissue slices and radioimmunoassay in cytosol. The first step involves isolation and purification of oestradiol receptor from human tumor tissue, using as starting material RE-c positive primary breast tumor obtained at mastectomy. After characterization, the receptor complex will be used to elicit antibody. Alternative methods which may prove to be more sensitive e.g., isoelectrofocussing in various matrices, are also being examined.

PROGRESS: The addition of nuclear receptor (RE-N) assay appears to reinforce the greater precision of prediction of response to hormone therapy in advanced breast cancer; this method involves measuring progesterone receptor as well as oestradiol receptor in the tumor cytosol.

Patients with RE-c positive RP-c positive primary tumors have been shown to have a longer disease-free interval than patients with RP-c negative tumors, irrespective of whether these were RE-c positive or RE-c negative. Both cytoplasmic assays and more recently the additional RE-N assay have been carried out on the tumors from 400-500 patients at mastectomy who are being followed for recurrence and subsequent response.

67. ENDOCRINE FACTORS INFLUENCING THE GROWTH OF TUMORS

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Antiestrogen therapy has yielded results equivalent to those of surgical hypophysectomy in the treatment of women with stage IV breast cancer. Antiestrogens have induced remissions in some 'completely' hypophysectomized patients in whom nevertheless low levels of estrogen were detectable in the serum. However, hypophysectomy has induced remissions after initial treatment with antiestrogen, suggesting that pituitary hormones may play a role in the growth of some breast cancers. Pharmacological doses of androgen have also been effective after antiestrogen therapy, suggesting that other endocrine factors may play a role. Antigrowth hormone, antiprolactin and antiandrogen drugs will be tested for potential antitumor effects. Estrogen, progesterone, androgen and prolactin receptors are being measured in the tumors for their potential usefulness in predicting response to endocrine treatment. The DMBA-induced rat mammary cancer model system is being used for studies on the regulation of receptor levels. Studies on combinations of endocrine and cytotoxic chemotherapy are being carried out in patients with stage II and stage IV breast cancer for the possible enhancement of therapeutic results.

68. DATA ANALYSES FOR BREAST CANCER TREATMENT PROGRAM

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The studies sponsored by the Treatment Committee fall into three categories: surgical adjuvant studies; estrogen recep-

tor studies; and tumor marker studies. The collection of clinical data allows a central file to be set up for all of these studies, permitting the comparison of results in a way which was not previously possible. Information is collected which describes patients at the time they are placed on study (e.g., age at diagnosis, menopausal status, tumor information) and, later, follow-up information (e.g., treatments, responses to treatments, metastases, date and cause of death) is collected.

69. ADVANCED BREAST CANCER - A STUDY OF ELASTOSIS IN PRIMARY TUMORS IN RELATION TO RECURRENCE RATE AND RESPONSE TO ENDOCRINE THERAPY

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More patients have now been included in this study. Results continue to indicate that the amount of elastosis in histological sections of primary carcinomas shows a positive correlation with response to endocrine therapy for advanced disease. Patients with no elastosis in their primary tumors show a lower rate of response than those with a gross amount of elastosis. In this series a combination of estrogen receptor status and elastosis assessment appears to be more accurate in predicting response to endocrine therapy than either factor taken alone. Patients with tumors containing estrogen receptor activity but having no elastosis show a similar low rate of response to endocrine therapy, as do patients with estrogen receptor-negative tumors. Evaluation of elastosis in primary breast tumors is also being correlated with recurrence rate in patients treated for early breast cancer.

70. TUMOR CHEMOTHERAPY - DIRECT EFFECT AND INDIRECT EFFECT BY HORMONE SUPPRESSION

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Since initiation of this study, 48 patients with disseminated breast carcinoma have consented to and have been entered into the study.

Estrogen receptor studies have been performed on tumor tissue from all 48 patients. We have collected, processed, and stored at minus 70 degrees C serial prechemotherapy and during chemotherapy plasma and serum samples from these 48 patients.

To date, only the radioimmunoassay for prolactin has been completed. Therefore, data is insufficient for conclusions.

71. STEROID BINDING IN BREAST CANCER BY IMMUNOFLUORESCENCE

Gaetjens, E., Pertschuk, L. P., Kim, D. S., Brigati, D. J., Carter, A. C., State University of New York, Downstate Medical Center, School of Medicine, Dept. of Pathology, *450 Clarkson Ave., Brooklyn, New York*, 11203, United States of America

A successful immunofluorescence technique for detection of estrogen receptor in human breast cancer has been developed. The method is based on the use of an estradiol polymer bound to the specific receptor on frozen sections of tumor. The polymer acts as a large antigen target for subsequent binding of antibody and labeled conjugate. We propose to synthesize water soluble polymers of progesterone, testosterone and glucocorticoid hormones suitable for use in immunofluorescence studies designed to detect specific receptor for these steroids in human mammary carcinoma. Results obtained by immunofluorescence will be compared with those of conventional biochemical assay and correlated with clinical response to therapeutic hormonal manipulations.

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72. THE GRADING OF MALIGNANCY OF HUMAN BREAST CANCER IN FINE NEEDLE ASPIRATES

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The objective of the program is to employ modern methods of cell biology to establish cytochemical and cytokinetic parameters that may be correlated with patients' eventual course. Cellular material is obtained by fine needle aspiration either at the time of first diagnosis or with subsequent surgical specimens.

The approach is to use markers such as determination of nucleic acids, in situ determination of RNA polymerase, growth potential, and biophysical measurements of dry mass in morphologically identified individual cancer cells and to correlate these values with prospective and retrospective survival studies.

Clinical data such as hormone receptor values and histopathological grading are also being sought. Developmental research is being conducted on cell viability, membrane characteristics and cytoskeletal characteristics.

PROGRESS: In 22 cases with metastases, patterns of distribution of nuclear DNA have been compared and it was found that recurrent breast cancers retain the same quantities of DNA even when recurring after many years. Short-term cultures have been established from 90% of the tumors examined and the characteristics of attachment have been studied. Estrogen receptor determinations in 56 cases have been compared with nuclear DNA amounts and a relationship between amounts of receptor and nuclear DNA distribution patterns has been found. These and other correlations are now being followed in a larger series of patients.

73. SPECIFIC MARKERS OF HORMONE-RESPONSIVE HUMAN BREAST CANCER

Thorpe, S. M., Daehnfeldt, J. L., Rose, C., Hansen, F. N., Briand, P., Fibiger Lab., *Ndr. Frihavnsgade 70, DK2100 Copenhagen, Denmark*

OBJECTIVE: To develop predictive tests for hormone responsive human breast cancer.

APPROACH: Closely connected with controlled clinical trials on the effect of endocrine treatment and/or chemotherapy, tumor tissue is being investigated for the content of estrogen and progesterone receptor protein by the dextran-charcoal method and prolactin binding to the crude membrane fraction. Free receptor sites as well as total receptor capacity have been determined.

74. BIOLOGIC MARKERS IN BREAST CANCER PATIENTS

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Determine the concentrations of a selected group of constituents in breast tissue obtained at mastectomy and to assay for these same substances in the serum of the patients obtained before their surgery and then sequentially on a scheduled basis over a period of time. Our aim is to find a constituent in cancerous breast tissue that is present in a concentration different from that in normal breast tissue and then to try to establish if changes in these concentrations in the breast tissue are reflected in the serum and whether the course of the disease is reflected in the serum pattern. We are now routinely obtaining in our laboratory breast tissue for analysis of estrogen receptor protein. It is our aim to determine in the cytosol and pellet of these tissues a variety of substances whose assays are in use in our laboratory. In addition, we can make available specimens for analysis in other laboratories.

75. RATIONAL DESIGN OF BREAST TUMOR LOCALIZING AGENTS

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A large number of human breast tumors contain estrogen receptors and, thus, have the ability to concentrate estrogenic substances. In principle, one should be able to utilize this selective uptake mechanism to concentrate a gamma-emitting radiopharmaceutical whose distribution could be monitored by gamma-imaging techniques. Such a procedure would provide a unique, non-invasive diagnostic tool for localizing breast tumors and metastases and determining their receptor content. This project is concerned with the synthesis and evaluation of such receptor-based, selective breast tumor localizing agents.

Halogenated derivatives (fluorine-18, bromine-77 and iodine-123) of various steroidal and non-steroidal estrogens will be prepared. The halogen will be placed at a position consistent with high chemical and metabolic stability and high receptor binding affinity, and the overall structure of the molecule will be designed to maximize its binding selectivity. This will be done by adjusting its structure to optimize its 'merit factor', which is defined as the ratio of its binding affinity for the estrogen receptor to its binding affinity for non-receptor proteins.

We have already prepared homologous series of iodostilbestrols and ring and side chain halogenated hexestrols; some of these compounds have merit factors in the 30-300 range. (The merit factor for estradiol is 100 by definition.) These compounds will be studied in vitro (receptor, serum, control and target tissue binding) and in vivo (tissue distribution and uptake selectivity) in animal model systems (DMBA-induced and R3230AC transplantable mammary tumor-bearing rats) to assess their feasibility as diagnostic agents for human breast cancer.

76. HORMONE DEPENDENCE IN ENDOMETRIAL AND BREAST CANCER

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The following investigations are proposed: 1. To quantitate the levels of estrogen and progesterone receptors in normal endometrium, hyperplastic endometrium, endometrial carcinoma, and breast carcinoma. The data will be used to evaluate the correlation of critical levels of estrogen and/or progesterone receptors in endometrial and breast tumors with the patients' response to endocrine therapy. 2. The association of estrogens with endometrial cancer will be examined by measuring estrone and estradiol levels in plasma, whole endometrial tissue and endometrial nuclei, as well as estrone-estradiol interconversions in the endometrium of patients with hyperplasia and carcinoma. 3. The mechanisms involved in the objective remission of endometrial tumors by progestational agents will be investigated by studying the following parameters in tumor tissue before and after progestin therapy: levels of estrogen receptors; levels of estrone and estradiol; estrone-estradiol interconversion; uptake and intracellular distribution of estrone and estradiol.

77. ADJUVANT THERAPY OF BREAST CANCER

Jerry, L. M., Geggie, P. H., Russell, J., Arthur, K., Pow, R. E., Francis, J. R., Alberta Provincial Cancer Hospitals Board, *2104 2nd St. SW, Calgary, Alberta, Canada*

The Southern Alberta Cancer Centre (SACC) (Calgary Cancer Clinic) has been a participating institution since July, 1977, in the National Surgical Adjuvant Breast Program Clinical Trials of adjuvant therapy for breast cancer. Until now we have been on subcontract with NSABP. Now that our ability to accrue patients has become established, NSABP has recommended that we apply for our own grant under their sponsorship. The SACC is situated in Calgary, and provides comprehensive cancer care to the southern half of Alberta and immediately adjacent regions. This represents a population base of approximately 1 million. About 60 new cases of Stage II breast cancer are seen at present at the Centre yearly, of which 40 are eligible for NSABP trials. Because of the rising incidence of breast cancer in the Province and its rapidly growing population, increasing numbers of new breast cancer patients are being seen here at the clinic each year. Because of manditory registration into a Provincial Tumor Registry we are able to accrue all of these eligible patients into trials, and are now following 20 patients in two NSABP protocols. Because of the oil industry Calgary is a boom town. Its population is expanding rapidly, as is the incidence of cancer in general and breast cancer in particular. A provincial laboratory provides hormone receptor assays, and the Centre is formally affiliated with the University of Calgary Faculty of Medicine for programs in Cancer Education and Research.

78. CLINICAL CANCER RESEARCH CENTER

Ultmann, J. E., University of Chicago, School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

The University of Chicago Cancer Research Center: Clinical Cancer Research Program is a multidisciplinary research effort encompassing diagnosis, staging, treatment, and correlations with basic science investigations in the following broad areas: (1) Breast Cancer -Pathologic evaluation of cases and correlation with estrogen receptors, lymph node morphology, and endocrine data will be continued; antibodies to receptor protein have been prepared and efforts to develop a radioimmunoassay will continue. (2) Gastrointestinal Cancer - The program to assess vulnerability of ulcerative colitis patients to cancer continues employing histologic and cytologic assessment with colonoscopy as well as studies of humoral and cell-mediated immunity. (3) Thyroid Cancer - Comparison of irradiated patients and patients who had thyroid carcinoma without history of irradiation continues. The immunologic status of thyroid cancer patients is being evaluated. TSH receptors on the surface of thyroid tumors will be studied. Immune complexes are being determined in the circulation of the patients. (4) Comprehensive Approach to Glioma Therapy - Kirsten virus induced brain tumors in rats are employed to study pathogenesis and test radio/chemotherapeutic interventions. A study of combined surgery, radiotherapy and chemotherapy with BCNU and epipodophyllotoxin is being completed. Glia maturation factor has been purified to homogeneity and specific antiserum is being obtained. (5) Lymphoma-Leukemia Program - Sensitive cellular assays measuring nanogram quantities of Ig have been developed to study B-cell function; T-cell cytotoxicity can also be assayed accurately. These techniques are used to study neoplastic lymphocytes. The project encompasses a determination of surface T- and B-cell markers, a cytogenetic analysis, the measurement and functional role of autologous serum immune complexes, and the determination of the effects of alpha-fetoprotein, an oncofetal protein, on the neoplastic cells contained in these separate lymphocytic malignancies.

79. EASTERN COOPERATIVE ONCOLOGY GROUP

Lerner, H. J., Zaren, H., Pennsylvania Hospital, Section of Surgical Oncology & Cancer Chemotherapy, *8th & Spruce Sts., Philadelphia, Pennsylvania*, 19107, United States of America

The major objectives are the overall objectives of the ECOG. These include: 1) The early evaluation of anti-cancer compounds. 2) The pharmacology, toxicology and efficacy of such compounds. 3) The acquisition of knowledge concerning the biology and patterns of expression of malignant disease.

Of additional particular interest to the principal investigator is: 1) Combination therapy (chemotherapy plus concomitant radiotherapy) in the management of locally advanced cancer. 2) The early chemotherapy of cancer when present but not yet measurable. 3) Large dose multi-drug chemotherapy of advanced cancers. 4) Interdisciplinary approach to care of the cancer patient. 5) Treatment of metastatic breast cancer with anti-estrogens (Tamoxifen) and its correlation to estrogen receptor proteins. 6) The use of WBC transfusions in septic, neutropenic patients. 7) The use of central and peripheral hyperalimentation in patients receiving multi-modal therapy, especially advanced head and neck cancers.

BIBLIOGRAPHIC REFERENCES: Vogl, S., McCormick, B., Coughlin, C.,*Lerner, H., and Kaplan, B. Chemotherapy with Cis-Platinum, Methotrexate and Bleomycin As Initial Treatment for Regionally Advanced Head and Neck Cancers. Submitted for presentation at the 62nd Annual Meeting of the American Radium Society, Philadelphia, PA, April 1980. Lerner, H., Carbone, P., and Kalbfleisch, J. Intermittent Parenteral Methotrexate (EST 2365). Submitted for presentation at the 16th Annual Meeting of the American Society of Clinical Oncology, San Diego, CA, May, 1980.

80. HISTOLOGICAL, CYTOLOGICAL AND HISTOCHEMICAL ALTERATIONS IN HUMAN MAMMARY CANCER

De Kastner, M. R., Schettino, A. M., Instituto Nacional do Cancer, *Praca Cruz Vermelha 23 ZC 86, Rio de Janeiro 20000, Brazil*

The purpose of this study is to analyze in detail the pathology of breast cancer. Particular attention is directed at: 1) Evaluating the morphology of the local cellular reaction in the breast and in the axillary lymph nodes. 2) Attempting the detection of tumor-associated antigens and steroid hormone receptors.

3) Searching for distinctive patterns helpful in differentiating histologic types of mammary cancer. 4) Determining the existence of an additional histologic index reflecting the degree of aggressiveness or a valuable prognostic meaning in breast cancer.

81. PREDICTION OF EVOLUTION OF BREAST CANCER AND RESPONSE TO TREATMENT

Diaz Gles Solis, J. W., Lage Davila, A., Pascual, M. R., Rios, M. A., Instituto de Oncologia y Radiobiologia, Laboratorio de Bioquimica, *Calle 29 y E Vedado, Havana 4, Cuba*

OBJECTIVE: To study the response to treatment and evolution of patients with breast cancer, by correlation with a select group of clinical and laboratory parameters.

METHOD: Studies of tumor differentiation and poliferation: Estrogen and progesterone receptors; index of labelling with thymidine; growth fraction. Studies of the characteristics of patients: PHA (blastic transformation); HLA (typing). Study of evolution and disease-free interval: CEA; serum fucose; serum ceruloplasmin and copper; others.

82. RATIONAL DESIGN OF BREAST TUMOR LOCALIZING AGENTS

Katzenellenbogen, J. A., Goswami, R., Allison, K. J., Heiman, D. F., Kilbourn, M. R., Ng, J. S., University of Illinois, Urbana-Champaign Campus, School of Liberal Arts & Sciences, Dept. of Chemistry, *Urbana, Illinois*, 61801, United States of America

A large proportion of human breast tumors contain estrogen receptors and, thus, have the ability to concentrate estrogenic substances. In principle, one should be able to utilize this selective uptake mechanism to concentrate a gamma-emitting radiopharmaceutical whose distribution could be monitored by gamma-imaging techniques. Such a procedure would provide a unique, non-invasive diagnostic tool for localizing breast tumors and metastases and determining their receptor content. This project is concerned with the synthesis and evaluation of such receptor-based, selective breast tumor localizing agents.

Halogenated derivatives (fluorine-18, bromine-77 and iodine-123) of various steroidal and non-steroidal estrogens will be prepared. The halogen will be placed at a position consistent with high chemical and metabolic stability and high receptor binding affinity, and the overall structure of the molecule will be designed to maximize its binding selectivity. This will be done by adjusting its structure to optimize its 'merit factor', which is defined as the ratio of its binding affinity to the estrogen receptor to its binding affinity to non-receptor proteins.

We have already prepared homologous series of iodostilbestrols and ring and side chain halogenated hexestrols; some of these compounds have merit factors in the 33-300 range. (The merit factor for estradiol is 100 by definition.) These compounds will be studied in vitro (receptor, serum, control and target tissue binding) and in vivo (tissue distribution and uptake selectivity) in animal model systems (DMBA-induced and R323OAC transplantable mammary tumor-bearing rats) to assess their feasibility as diagnostic agents for human breast cancer.

83. ENDOCRINE RESPONSIVENESS IN PATIENTS WITH BREAST CANCER

De Kastner, M. R., Schettino, A. M., Instituto Nacional do Cancer, *Praca Cruz Vermelha 23 ZC 86, Rio de Janeiro 20000, Brazil*

There is considerable evidence that the actions of all steroid hormones on their target cells are mediated, at least in part, through their interaction with receptor proteins. Since conventional methods at the present time for biochemical receptor assay are expensive and require preparation of tumor cytosol by ultracentrifugation, radiolabeled chemicals and scintillation counting, it is vital that methods should be developed for the detection of these receptors suitable for performance in the average community hospital

The purpose of this preliminary study is: 1) To explore the possibility of an immunofluorescent staining method that can be applied to surgical specimens from breast cancers. 2) To study the heterogeneous tumor cell populations in terms of ER and PgR levels. 3) To demonstrate the real significance and role of ER and PgR measurement. 4) To evaluate the correlation between the presence of tumor ER and PgR and the response to endocrine therapy.

84. ESTRADIOL SENSITIVE MAMMARY CANCER AND LOCALIZATION WITH 197 HG-LABELLED 4-MERCURY-ESTRADIOL

Doorenbos, H., Oldhof, J., Woldring, M. G., Janssens, J., Pratt, J. J., Feenstra, A., University Hospital of Groningen, Dept. of Nuclear Medicine, *Oostersingel 59, Groningen, Netherlands*

OBJECTIVE: The in vivo localization of breast cancer containing estrogen receptors with 197 Hg-labelled mercury-17-beta-estradiol.

APPROACH: The synthesis of 197 HG-labelled mercury-17-beta-estradiol with a high specific activity on a very small scale, and the characterization of the interaction of the product with the cytoplasmic and nuclear estrogen receptor.

85. PREDICTION OF RESPONSE TO ADRENALECTOMY

Jensen, E. V., University of Chicago, School of Medicine, Dept. of Physiology, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

GOAL: To develop, improve and evaluate techniques that will increase the predictability of response of human breast cancers to endocrine therapy.

WORKSCOPE: Since 1966, Dr. Jensen has been studying estrogen receptors (ER) in human breast cancer tissues and the relationship between ER content and response to endocrine manipulative treatments. Now that the predictive value of ER measurements has been established, attention is being directed toward development of simple, inexpensive assay procedures for ER in breast cancers and evaluation of the ability of an ER assay on the primary tumor, carried out at the time of mastectomy, to predict subsequent response to endocrine therapy.

B. OTHER ENDOCRINE PARAMETERS IN DIAGNOSIS, PROGNOSIS, AND TREATMENT SELECTION

86. METABOLISM OF ESTROGENS AND ANDROGENS BY BREAST CANCER CELLS

MacIndoe, J. H., Sherman, B. M., Granner, D. K., Ginsberg, B. H., University of Iowa, School of Medicine, Dept. of Internal Medicine, *Jessup Hall, Iowa City, Iowa*, 52240, United States of America

Continuously cultured MCF-7 human breast cancer cells have been recently reported to be responsive to both androgens and estrogens. Studies in this laboratory have confirmed the presence of several enzymes in this cell line that allow the intracellular synthesis of biologically active androgens and estrogens from extracellular precursor steroids. The objectives of this proposal are to 1) identify the spectrum of steroids capable of being transformed by this cell line to active sex steroids and 2) determine whether or not intracellular sex steroid formation can maintain hormone-dependent events in this cell line. Studies include the determination of 5-alpha-reductase, 3-hydroxysteroid dehydrogenase, aromatase, and 17-beta-hydroxysteroid dehydrogenase activities in both whole cultures and cell free MCF-7 systems under a variety of substrate conditions. Studies will also invplve examining the effects of various single and combined steroid treatments upon cell protein, steroid enzyme, and DNA contents, as well as alterations in cellular progesterone, estrogen, and androgen receptor levels.

Several studies report that some human breast tumors are capable of forming androgens and/or estrogens from extracellular precursor. However, investigations into the relative importance of these phenomena in regulating sex hormone dependent cell growth have been hampered by the lack of a suitable model. Our studies now indicate that MCF-7 cells should provide such a system. We anticipate that the results of this study will provide additional insights into the hormonal regulation of human breast cancers, which may eventually lead to improved cancer therapies.

BIBLIOGRAPHIC REFERENCES: MacIndoe, John H., Estradiol Formation from Testosterone by Continuously Cultured Human Breast Cancer Cells, J. Clin. Endocrinol. Metab. 49:272, 1979.

87. CLINICAL PROGRAM IN BREAST CARCINOMA

Lippman, M. E., Cassidy, J., Simon, R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medical Breast Cancer Section,

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The Medical Breast Cancer Section is responsible for the development of a clinical and laboratory program directed at breast cancer. Clinical trials in metastatic disease comparing chemotherapeutic, hormonal and chemohormonal regimens are under way. Biochemical and hormonal marker studies are undertaken and coordinated by the Medical Breast Cancer Section. These studies consist of a major chemotherapy trial aimed at synchronizing human breast cancer cells with hormonal agents for more successful cell cycle phase specific chemotherapy; a hormonal therapy trial aimed at prospectively evaluating the usefulness of steroid receptors for estrogens, androgens and progestins in human breast cancer; an advanced disease hormonal therapy trial comparing tamoxifen to tamoxifen plus an androgen; several phase II trials including (DDP is completed) chlorozotocin; and an endocrine therapy trial in male breast cancer.

BIBLIOGRAPHIC REFERENCES: Allegra, Joseph C. and Lippman M.E.: Chemotherapy for breast cancer, Cancer, 5: 13-16, 1979. Lipsett, M.D. and Lippman, M.E.: Endocrine responsive cancers of man in Endocrinology, ed by R.H. Williams and W.B. Saunders, Philadelphia, 1979, (in press).

88. SPECIALIZED CENTER FOR CANCER ENDOCRINOLOGY

Fishman, J., Kappas, A., Bradlow, H. L., Fishman, J. H., Martucci, C., Norton, B., Ikegawa, S., Tsukamoto, T., Fukushima, D. K., Rosenfeld, R. S., O'Connor, J. F., Lewis, J. L., Rockefeller University, University Hospital, *66th & York Ave., New York, New York,* 10021, United States of America

Radiometric studies on the biosynthesis and principal metabolic pathways of estrogen and androgens in patients with breast, endometrial and prostate cancer will be continued and the results compared with those obtained in normal subjects. The impact of endocrine therapy on these transformations will be followed to determine whether any correlations exist. The properties of receptors in human breast, endometrial and ovarian tumor tissues will be explored, with particular emphasis on the heterogeneity of these receptors. These differences in receptor properties will be correlated with the clinical history of the patients.

Studies on the pathways of estradiol biosynthesis and on the role of its transformation products produced in situ on the biological responses observed in various target sites will also be continued.

The mechanisms of formation and the role of the novel cortoic acids will remain an active area of study. New methods for the quantitation of these compounds are being explored.

Studies on the mechanism of entry of hormones into human breast cysts will be continued.

Studies of the influence of drugs and diet on the metabolism of estradiol in normal patients will be carried out to determine the influence of these compounds on the pathways of metabolism of estradiol in order to seek a relationship between diet or drugs and cancer risk.

BIBLIOGRAPHIC REFERENCES: 6-Aminoalkyl catechol estrogens - Models of steroidal biogenic amines. A. Takadate and J. Fishman, J. Org. Chem. 44: 67, 1979. Low urinary estrogen glucuronides in women at risk for familial breast cancer. J. Fishman, D. Fukushima and H. Lynch, Science 204: 1089, 1979.

89. SIGNIFICANCE OF ALTERED TSH SECRETION

Maloof, F., Ridgway, E. C., Kieffer, J. D., Chin, W. W., Cooper, D. S., Habener, J. F., Massachusetts General Hospital, Dept. of Medicine, *32 Fruit St., Boston, Massachusetts,* 02114, United States of America

Alterations in the biosynthesis, secretion, and regulation of TSH and its subunits occur in patients with disorders of the thyroid-pituitary axis. To define these abnormalities, one must understand the molecular events involved in the biosynthesis of TSH and its subunits.

TSH is one of a family of glycoprotein hormones that consists of two non-covalently linked, dissimilar subunits, designated alpha and beta. We propose to investigate the cellular events that take place in the biosynthesis of TSH. We wish to determine how these processes are regulated, how they may be interdependent, and how they may be involved in intracellular transport, packaging, and secretion of hormone. The isolation of mRNA coding for the TSH subunits and the production of cDNA to mRNA will allow study of the translational and transcriptional process. In addition, pulse-chase labeling experiments in intact cells will allow study of the post-translational processes. These initial studies will then provide the basis for subsequent studies of the cellular mechanisms involved in the regulation of subunit synthesis, assembly, and secretion mediated by thyrotropin-releasing hormone and thyroid hormones.

We will also investigate TSH and subunit secretion in the normal thyrotroph using the bovine anterior pituitary cell culture systems.

In our clinical approach, we will determine the long-term metabolic consequences of slight and variable decreases in the serum concentration of T4 and T3 and concomitant increases of TSH for: (a) cardiovascular system, (b) pituitary function and size (tumor), and (c) breast abnormalities, including breast cancer. We plan to expand our investigations of the unbalanced alpha subunit secretion by pituitary tumors in patients in order to evaluate the efficacy of subunit measurements in early diagnosis and effective therapy. In addition, immunochemical and physicochemical properties of subunits secreted by pituitary tumors will be evaluated to elucidate similarities or differences in the biosynthesis of the glycoprotein from normal and malignant pituitary cells.

BIBLIOGRAPHIC REFERENCES: Cooper, D.S., Kaplan, M.M., Ridgwa, E.C., Maloof, F., and Daniels, G.H.: Alkaline phosphatase isoenzyme patterns in hyperthyroidism. Ann. Int. Med 90: 164-168, 1979. Ridgway, E.C., Kourides, I.A., Chin, W.W., Cooper, D.S., and Maloof, F.: Augmentation of pituitary TSH response to TRH during subphysiological triiodothyronine therapy in hypothyroidism. Clin. Endocrinol. 10: 343-353, 1979.

90. SEX STEROID BIOSYNTHESIS AND ACTION IN HUMAN BREAST CANCER

MacIndoe, J. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Hwy. 6 W., Iowa City, Iowa,* 52240, United States of America

PROJECT OBJECTIVES: To 1) identify steroidogenic enzymes in MCF-7 human breast cancer cells, 2) investigate the relative activities and hormonal regulation of enzymes involved in androgen and estrogen biosynthesis, and 3) determine the effects of intracellularly formed sex steroids upon cellular metabolism.

PLAN: MCF-7 breast cancer cells are being examined for androgen and/or estrogen synthetic capability using radiolabeled precursor steroid, and established enzyme assay techniques. Once identified, each steroidogenic enzyme is being characterized as to its intracellular location, substrate requirements, and potential hormonal regulation. Other studies are investigating the effects of estrogens, androgens, and combined sex steroid treatment upon specific cellular functions. This data will be used to determine whether or not intracellular sex steroid synthesis can influence MCF-7 metabolism and the relationship between these responses and the nature of the extracellular steroid environment.

METHODS: Cell culture, thin-layer chromatography, double isotope derivative steroid purification, steroid hormone receptor assay.

FINDINGS TO DATE: (1) MCF-7 cells contain aromatase, 5-alpha-reductase, 17-beta hydroxysteroid dehydrogenase, and 3-hydroxysteroid dehydrogenase. (2) Some androgens block estrogenic stimulation of cytoplasmic progesterone receptor. These data suggest that sex steroid synthesis and subsequent action within MCF-7 cells may depend upon the type and quantity of extracellular precursor and the relative activities of several intracellular enzymes.

CLINICAL IMPORTANCE: This work is of importance to the area of hormone dependent human breast cancer therapy and of significant potential importance to clinical disorders associated with altered sex steroid metabolism such as aging and alcoholism.

91. STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

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Our main activity involves the study of the hormone calcitonin. We are currently exploring the physiochemical state of calcitonin in the blood. We have developed a sensitive radioreceptor assay for the hormone, in order to determine which of the heterogenous serum fractions react with receptor. We have developed a radioimmunoassay for calcitonin in the urine, and have found it to be of considerable value in the diagnosis of medullary thyroid cancer. We have found that large amounts of calcitonin exist in several tissues other than the thyroid gland, and we are exploring the nature of the extrathyroidal hormone. In addition, we are utilizing serum and urinary calcitonin as a label for lung cancer and breast cancer.

92. HORMONE PRODUCING NONENDOCRINE TUMORS

Samaan, N. A., Yang, K. P., Hill, C. S., Hickey, R. C., Ward, D. N., Rutledge, F. N., Smith, J. P., Blumenschein, G. R., Copeland, E. M., Jesse, R. H., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Medicine, *c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

Hormone production by nonendocrine tumors may serve as a marker for early detection. 1) Hormone production by nonendocrine tumors will be measured in peripheral circulation, in affluent and effluent blood obtained at catheterization under fluoroscopy or at surgery in tumor and control tissues. 2) The effects of various methods of therapy on hormone production with progression or regression of the disease will be determined. 3) The effect of certain cancers on hormone secretion by endocrine organs will be studied. 4) The endocrine disturbances which may result as side-effects of different methods of therapy of cancer will be studied. 5) Effect of parenteral hyperalimentation on circulating hormone levels will be evaluated. 6) On detection of hormone producing tumors, the tumors will be extracted directly or cultured in vitro to secrete the hormones. The substances thus obtained are then tested for their physical and chemical properties. Chemical and physical characterization including Sephadex gel- and ion-exchange chromatography will be conducted where practical to compare the molecular size of nonendocrine tumor hormones with native hormones. 7) Localization of hormone production by the tumor will be done by immunohistochemistry. 8) Identify and quantitate the specific hormone receptors in breast and endometrial carcinoma. 9) Investigate the effects of prolactin and other polypeptides and steroid hormones on the growth of breast cancer cells in culture. 10) Study the hormonal changes which might occur with adjuvant chemotherapy in treatment of breast cancer patients and correlate the course of the disease with the hormone profile in these patients.

93. STUDY OF SOME RELATIONSHIPS BETWEEN ESTROGEN METABOLITES AND BREAST CANCER

Cohen, S. L., University of Toronto, Dept. of Obstetrics & Gynecology, *92 College St., Toronto, Ontario*, M5S 1B2, Canada

OBJECTIVES: a) To determine a possible relationship between breast cancer and the occurrrence of 2-hydroxy (catechol)-estradiol in the urine. Preliminary observations tend to indicate such a relationship. b) To determine the nature of the estrogen bound to the nuclear receptors of breast cancer tissue. Preliminary observations indicate that it is either estriol or 2-hydroxy-estradiol (our conditions of assay did not exclude either of these).

APPROACH: a) To carry out our 'profile' assay technique (Cohen et al., Steroids 32, 279, 1978) on urines from patients with breast cancer and a wide variety of controls: normal cycling women; post-menopausal, less than 5 years, 5-10 years, and more than 10 years; women of all ages being subjected to other surgeries. b) To have the catechol estrogens assayed by the specific mass-spectrometric technique of Rosenberg (Hamilton). c) To assay the catechol estrogens by radioimmunoassay techniques (3 different groups of workers have described such a technique).

PROGRESS: April 1-August 31, 1979: a) We have assayed 15 urines (every other day) from the complete 28-30 day cycles of 3 young women. The assays are presently being checked for me by Dr. Diemunn of the Mass. Inst. of Tech. in Boston, by mass-spectrometry. b) An organic chemist (Pauline Zvirsky) is well into the preparation of large quantities of the 3 catechol estrogens for use in the preparation of antibodies. c) I am about to hire someone for the tissue work. Since tissue estrogen assays involve assays which are in the 10 to the minus 6th to the minus 9th power of those in urine, we do not like to do both assays in the same room. So we have arranged to have the tissue assay work conducted in Dr. Mobb's laboratory. The NCI Grant does not permit payment of a technician for more than 1/2 time. So I am hiring someone for 1/2 year on the current grant and 1/2 year on next year's grant. She (he) will thus be able to work full time on the project.

94. STUDY OF STEROID SULFATION AND ESTROGEN BINDING

Dao, T. L., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

The specific aims are: To correlate the steroid sulfotransferase activity and estradiol binding proteins in the primary tumor at the time of mastectomy with pathological staging of the disease and the rate of recurrence and to evaluate whether measurement of these biochemical parameters is useful for predicting response to endocrine ablation when metastasis occurs in these patients.

95. STUDIES ON URINARY STEROID ANALYSIS IN BREAST CANCER PATIENTS

Kodama, M., Kodama, T., Aichi Cancer Center Research Inst., Laboratory of Chemotherapy, *81-1159 Kanokoden Tashiro-cho, Chikusa-ku, Nagoya 464, Aichi, Japan*

OBJECTIVE: To demonstrate steroidal characteristics of a breast cancer patient which are correlated with the initiation and further development of breast neoplasia.

APPROACH: Profile analysis of neutral steroids with gas chromatograph. Urine specimen is processed by Horning's method before GLC analysis.

BIBLIOGRAPHIC REFERENCES: Journal of the National Cancer Institute 59: 49-54, 1977. Hormonal status of breast cancer.

96. THE ROLE OF PROSTAGLANDINS IN TUMOUR GROWTH AND SPREAD

Bennett, A., Harris, M., University of London, King's College Hospital Medical School, Dept. of Surgery, *Denmark Hill, London SE5 8RX, England, United Kingdom*

OBJECTIVE: To evaluate further the relationship of prostaglandins to growth of human tumors and their spread, in particular to bone. By following up patients already studied, it will be possible to determine whether tumor prostaglandin production can be used to predict those patients at the risk of osseous metastases. The types of prostanoids formed by human tumors will be formally identified.

APPROACH: The prostaglandins formed by human tumors are measured by bioassay, and in some cases formal identification is made with mass spectrometry. These findings are related to tumor histology, bone scanning and patient survival. Other studies are in progress to investigate formation of prostanoids from labelled and unlabelled prostaglandin precursors.

PROGRESS: There seems to be a correlation between tumor prostaglandin production, tumor invasiveness, the incidence of bone metastases and early patient death from cancer following breast surgery.

A substantial amount of information has been obtained on other tumors, and these are in the process of being analyzed.

97. INVESTIGATION OF ESTROGEN-NITROSOUREA CONJUGATES WITH POTENTIAL SPECIFIC ANTITUMOR ACTIVITY

Lam, H. P., Manitoba Inst. of Cell Biology, *700 Bannatyne Ave., Winnipeg, Manitoba*, R3E 0V9, Canada

OBJECTIVE: This project aims to test the hypothesis that specific antitumor activity may be achieved by taking advantage of the presence of receptors with specific binding properties,

which might result in selective accumulation of cytotoxic agents in ER-positive mammary tumors.

APPROACH: Some estrogen-nitrosourea conjugates will be synthesized. They will be tested against ER-positive and ER-negative mammary tumor cell lines in vitro and in vivo.

98. HORMONAL PATTERN IN INFLAMMATORY BREAST CARCINOMA

Kiricuta, I., Frenkel, Z., Institutul Oncologic Cluj-Napoca, Hormonal Laboratory, *34-36 Republicii, 3400 Cluj-Napoca, Romania*

OBJECTIVE: Comparative characterization of hormonal pattern in inflammatory breast carcinoma and in breast cancer with slower evolution, in view of a possible use of results in therapy and prognosis of these diseases.

RESEARCH METHODS: The urinary excretion of some steroid hormonal metabolites with spectrophotometric methods both in a group of patients with inflammatory breast carcinoma and in a group with normal evolutive breast cancer. Determinations are carried out for the 24 hr urine (for those in menstrual cycle on the 14th day of cycle). The analysis of total 17-ketosteroids is performed according to a variant of the Zimmermann method and determination of fractionated 17-ketosteroids is carried out by chromatography in thin layer of silica gel. Determination of total estrogens is performed by a variant of the Yayle method. The experimental results are statistically estimated.

PRELIMINARY RESULTS: The data of a limited number of patients show more enhanced hormonal imbalance in inflammatory breast carcinoma than in normal evolutive breast cancer.

99. PROSPECTIVE INVESTIGATION OF ENDOCRINOLOGICAL FACTORS IN BREAST CANCER

Stax, P., Bulbrook, R. D., Hayward, J., Kwa, H. G., Stella & Charles Guttman Breast Diagnostic Inst. Inc., *200 Madison Ave., New York, New York*, 10016, United States of America

This study comprises a prospective investigation of endocrinological factors involved in initiation or promotion of breast cancer. Some 30,000 women, both premenopausal and postmenopausal, will have a complete breast examination, including questionnaire, clinical examination, mammography and thermography. Blood examinations will involve androgens, progesterone and prolactin. A pilot project involving 1,000 women began in April 1979.

100. IMMUNOASSAY OF CALCITONIN

Becker, K. L., Silva, O. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Metabolic Section, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

We are pursuing our studies of the pathophysiology of calcitonin, utilizing the radioimmunoassay we have developed for the hormone in serum and urine. Our ongoing studies of bronchogenic cancer demonstrate that serum calcitonin is a clinically useful marker for this tumor, and that serum levels often decrease concomitantly with chemotherapy and/or radiotherapy. We are continuing our study of calcitonin in breast cancer in cooperation with Howard University; thus far, high serum levels are encountered in untreated women with metastatic disease, in contrast to the normal levels usually seen in those with localized disease. It is possible that high calcitonin levels in the presence of a breast cancer may indicate that extensive mastectomy should not be performed.

The newest tool in our armamentarium to study calcitonin pathophysiology is a specific, sensitive radioimmunoassay to measure calcitonin in the urine. This assay is simple, reproducible and allows for removal of interfering substances which complicate the serum assay. We have found this test extremely useful in the evaluation of patients with medullary thyroid cancer. Many patients, with normal serum calcitonin, have high urinary calcitonin.

We have found that calcitonin persists in the blood and urine of totally thyroidectomized humans. In an autopsy study, we find that calcitonin has a widespread distribution in many tissues other than the thyroid gland. We have recently completed an experiment in which the extrathyroidal tissues of monkeys continue to contain large amounts of calcitonin two months following total thyroidectomy. The demonstration of extrathyroidal calcitonin explains why thyroidectomy is not associated with any profound changes in calcium or phosphate metabolism.

101. CALCITONIN AS A MARKER FOR CANCER OF THE BREAST

Silva, O. L., Becker, K. L., Chisholm, R., Howard University, School of Medicine, Dept. of Medicine, *2400 6th St. N.W., Washington, District of Columbia*, 20001, United States of America

Using a sensitive and specific radioimmunoassay we have developed for the determination of human calcitonin (HCT) in unconcentrated peripheral blood, we propose to study HCT levels in patients with cancer of the breast. Calcitonin is a hypocalcemic, hypophosphatemic polypeptide hormone secreted by C cells of mammalian thyroid. In 1973, we reported finding increased levels in 35% of cancer patients with spontaneous hypercalcemia. During a study of normocalcemic patients with bronchogenic cancer, it became apparent that over 69% of these patients had calcitonin levels above normal. Was this hypercalcitonemia a response to bone resorption and impending hypercalcemia? Could calcitonin be used as a marker in cancer? Coombes et al. confirmed the high incidence of hypercalcitonemia in bronchogenic cancer and, in addition, showed that 100% of the breast cancer patients with skeletal metastases, studied by them, had high values of blood calcitonin which could be augmented by calcium infusion. In our laboratory a preliminary study of 13 women with metastatic breast cancer in the clinic at the Howard University Hospital showed that 69% had elevated HCT levels. (Many of these patients had undergone prior therapy). We intend to correlate HCT levels with the duration of disease, disease-free period, presence and extent of bone metastases, presence of extra-skeletal metastases, effect of therapy and prognosis. Perhaps HCT may prove to be a marker for breast cancer.

BIBLIOGRAPHIC REFERENCES: Silva, O.L., Baylin, S., Wells, S., Snider, R.H., Moore, C.F. and Becker, K.L.: Urinary calcitonin as a test for medullary thyroid cancer: a new screening procedure, Ann. Surg. 189(3): 269-274, 1979. Becker, K.L., Bivins, L.E., Radfar, R.H., Snider, R.H., Moore, C.F. and Silva, O.L.: Study of calcitonin heterogeneity using a radioreceptor assay. Horm. Metab. Res. 10(5): 457-458, 1978.

102. ROLE OF ESTROGEN AND OTHER HORMONES IN BREAST CANCER

Butler, W. B., Kelsey, W., Goran, N., Michigan Cancer Foundation, Dept. of Chemistry, *110 E. Warren St., Detroit, Michigan*, 48201, United States of America

The summary for this project is under entry no. 60.

103. STEROID RECEPTORS AND INDUCIBLE PROTEINS IN BREAST TUMORS

Duffy, M. J., O'Connell, M., St. Vincent's Hospital, Dept. of Nuclear Medicine, *Elm Park, Dublin, Ireland*

The summary for this project is under entry no. 61.

104. TUMOR CELL CHARACTERIZATION BY FLUORESCEIN ESTRADIOL

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The goals of this proposal are to detect, to quantitate and to separate cells or nuclei containing estrogen receptors by a flow fluorometer. The cells or nuclei will be derived from three sources: nine established human breast cell lines, tissue from immature rat uteri, and human breast cancer tissue. A prepared fluorescein labeled estradiol which competes with 3H-estradiol for receptor binding sites, will be incubated with cellular or nuclear suspension to form a steroid-receptor complex. This complex in the cells or nuclei will then be analyzed and/or separated by the degree of fluorescence which would be directly related to the receptor concentration. This procedure would quantitate the receptor concentration on a cellular basis (percentage of cells that are estrogen receptor positive) rather than a cytosol protein concentration parameter. Receptor concentration determined by standard radioactive procedures would be correlated with all fluorescence determinations in order to standardize the fluorescent data and both parameters would be related to responsiveness of patients treated with hormonal therapy. Futhermore, the cell cycle kinetics will be determined by

DNA histograms using the flow fluorometer and this data compared to estrogen receptor concentrations. Subsequent to sorting the estrogen receptor positive cells or nuclei (high fluorescence) from the estrogen receptor negative cells or nuclei (low fluorescence), these two populations will be studied by electron microscopy cell culture techniques and DNA content. The fluorescence assay described above has many advantages over the standard 3H-steriod procedures presently used for steroid receptor analysis. It is fast, sensitive and able to use small amounts of tissue. The principal investigator also believes that it would be more diagnostic of tumor type and therefore, serve as a better indicator for hormone responsiveness in breast cancer patients.

105. ASSESSMENT OF THE MODIFIED C1Q BINDING ASSAY AS AN AID TO DIAGNOSIS IN A BREAST CANCER SCREENING PROGRAM

Baldwin, R. W., Blamey, R., Robins, R. A., University of Nottingham, Cancer Research Campaign Lab., *University Park, c/o City Hospital, Nottingham NG7 2RD, England, United Kingdom*

OBJECTIVE: To evaluate serum immune complex assays as an aid in breast cancer screening.

APPROACH: Circulating immune complexes (CIC) are being evaluated by C1q binding assay in sera from patients with breast cancer and individuals attending a breast screening clinic. From these studies it is projected that the assay will be able to distinguish patients with malignant breast disease from those with benign breast diseases. In addition to using the C1q binding test, tests are also to be carried out for evaluating other methods for determining CIC. Current research is being directed towards the evaluation of a conglutinin assay.

106. EFFECT OF PROGESTATIONAL AGENTS IN BREAST CANCER (HUMAN)

Cox, C. E., Duke University, School of Medicine, Dept. of Surgery, *Box 3711, Durham, North Carolina*, 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

C. IMMUNOLOGICAL TECHNIQUES FOR DIAGNOSIS AND PROGNOSIS OF BREAST CANCER

107. BREAST NEOPLASIA DIAGNOSIS WITH SPECIFIC ANTIBODIES

Ceriani, R. L., Peterson, J. A., Sasaki, M., Childrens Hospital Medical Center of Northern California, Bruce Lyon Memorial Research Laboratory, *51st & Grove Sts., Oakland, California*, 94609, United States of America

Antibodies against cell-type specific antigens on the surface of mammary epithelial cells (both in humans and in mice) are used for the development of diagnostic procedures for the early and specific detection of breast cancer. These mammary epithelial antigens are shown, by indirect immunofluorescence, to be present on breast cells both in vivo and in vitro, irrespective of their origins (normal or neoplastic breast tissue). They are not detected on cells from other tissues. By quantitative techniques that we have developed to measure these antigens on a cell per cell basis using the flow cytofluorometer, we have shown that neoplastic breast epithelial cells contain levels of mammary epithelial antigens per unit DNA several fold less than levels in normal breast cells. We have also developed very sensitive radioimmunoassay techniques, with which we have established that mammary epithelial antigens are released into circulation of mammary tumor-bearing mice, but not in normal mice. This finding sets the basis for the development of mass screening methods for early detection of breast cancer, since the radioimmunoassay is a simple, inexpensive and highly sensitive procedure. Also, methods are being developed for the localization of breast cancer metastases by whole body scintiscanning techniques using radioactively labeled antibodies against the breast epithelial antigens.

BIBLIOGRAPHIC REFERENCES: Wilbanks, T., Peterson, J. A., Miller, S., Kaufman, L., Ortendahl, D. and Ceriani, R. L. Imaging of Mammary Tumors with Cell-type Specific Antibodies with a High Purity Germanium Camera. Presented at Radioimmunochemical Detection of Cancer: A Symposium, Albuquerque, New Mexico, December 1979, in press. Fentiman, I. S., Hurst, J., Ceriani, R. L., Taylor-Papadimitriou, J. Junctional Intercellular Communication Pattern of Cultured Human Breast Cancer Cells. Cancer Research 39:4739-4743, 1979.

108. ANTIGEN-ANTIBODY COMPLEXES IN BREAST CANCER

Chu, T. M., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

The objective of this study is to assay soluble antigen-antibody complexes in serum of patients with breast cancer using C1q binding radioimmunoassay, Raji cell radioimmunoassay, and (rabbit) rheumatoid factor assay. The serum specimens will be obtained from breast cancer patients, fibrocystic breast disease patients and breast cancer families as well as from appropriate healthy control individuals. The breast cancer patients will be longitudinally followed for evaluation of the response to treatment in order to determine the prognostic and monitoring values of the assay. The high risk groups (fibrocystic breast disease and breast cancer families) are also to be followed in order to evaluate the diagnostic potential of the immune complex assay. The antigen-antibody complexes are also to be isolated from the serum and body fluids (pleural effusion) of breast cancer patients by molecular exclusion chromatography, protein A affinity chromatography and immunoadsorption using affinity media to the Fc domain of IgG. Further, the isolated immune complexes will be dissociated under the least denaturing conditions. The dissociated antigens are to be characterized biochemically and immunologically. Xenobiotic antisera will be raised with the dissociated antigen(s) and with isolated complexes as well as with the Raji cells containing surface-bound immune complexes injected into rabbits made tolerant to human IgG, and studied by their ability to recombine the dissociated antigen and to bind malignant breast tissues. In vitro antibody-dependent cell-mediated cytotoxicity, lymphocyte mitogenesis, PHA-induced lymphocyte blastogenesis and LAI assays are also to be performed to study the possible biological function of antibody-antigen complexes. Further, a radioimmunoassay will be developed which may be of use in early detection and monitoring of efficacy of therapy for breast cancer.

109. DETECTION OF ANTIGEN-ANTIBODY COMPLEXES IN BREAST CANCER

Medof, M. E., University of Chicago, School of Medicine, Dept. of Medicine, *5801 S. Ellis Ave., Chicago, Illinois*, 60637, United States of America

OBJECTIVES: Assay a statistically adequate number of sera from patients with breast cancer, benign breast disease, and normal volunteers for IC's by employing multiple techniques for IC detection and quantitation which have been developed in and are currently in operation in our laboratory. Our multiple techniques will permit differentiation between soluble and insoluble IC's and between complement bearing and IgG-Fc accessible IC's. To correlate presence or absence, or levels where applicable, of individual IC subpopulations with tumor progression, response to therapeutic intervention, and clinical course, otherwise. Data will be analyzed according to clinical stage of the patient, histologic type of the tumor, histology of regional lymph nodes, ovarian and other hormonal status of the patient, and the presence or absence of estrogen receptors on tumor cells.

110. PURIFICATION OF BREAST TUMOR ASSOCIATED ANTIGENS

Oldham, R. K., Vanderbilt University, School of Medicine, Dept. of Medicine, *21st Ave. S. & Garland, Nashville, Tennessee*, 37232, United States of America

OBJECTIVE: Isolate and purify the tumor associated antigen of the MCG-7 breast cancer derived tissue culture line for use in generating heteroantisera, to lead to the development of a radioimmunoassay for that antigen for use in immunological testing of patients with premalignant breast disease as well as patients with clinical carcinoma of the breast. Plans for monitoring of the antigen during purification and for analysis of clinical data shall be provided to the project officer for approval before such work is under way.

111. STUDY OF CIRCULATING IMMUNE COMPLEXES IN CANCER

Masson, P. L., Cambiaso, C. L., Universite Catholique de Louvain, Experimental Medicine Unit, *75 Ave. Hippocrate, B1200 Brussels, Belgium*

OBJECTIVE: To assay and isolate antigen-antibody complexes in the circulation of cancer patients, and to isolate, identify and characterize constituents of the complexes.

APPROACH: The antigen-antibody complexes are detected by inhibition of the agglutinating activity of rheumatoid factor or C'9 IgG-coated particles. The agglutination is measured by counting the non-agglutinated particles in a Technicon Autocounter designed to count blood cells. The method is tested by reference to the results obtained by sucrose gradient ultracentrifugation, which is also used for the isolation of complexes.

PROGRESS: The agglutination inhibition test is now operational and routinely used at a sampling rate of 40/hr. Preliminary data obtained in lung and breast cancer indicate that the level of circulating immune complexes correlates to some extent with tumor burden.

112. HLA ANTIGENS AND SURVIVAL IN MAMMARY CARCINOMA PATIENTS

Pellegris, G., Muscolino, G., Bertario, L., Costa, A., Illeni, M. T., Leo, E., Saccozzi, R., Istituto Nazionale per lo Studio e la Cura dei Tumori, Immunohematology Laboratory, *1 Via G Venezian, 20133 Milan, Italy*

OBJECTIVE: The aim of this work is to verify HLA typing as to whether immunogenetic factors may be suspected as playing any role in conditioning the survival of patients for over 8 years after surgical removal of mammary carcinoma.

APPROACH: Two groups of patients will be typed for HLA A,B and C antigen: one group showing relapse and/or metastasis more than 8 years after surgical removal of the tumor, the other being apparently free of tumor clinical signs. Each group will include 30 to 50 patients untreated by chemo- and/or hormonotherapy.

The lymphocytotoxic test will be used.

Controls will be healthy unrelated females, similar to the patients as regards age, and living in the same geographical area as the patients.

113. LOCALIZATION OF ANTI-CEA ANTIGEN AND ANTI-CDP ANTIBODIES IN BREAST CANCER

Cox, C. E., Duke University, School of Medicine, Dept. of Surgery, *Box 3711, Durham, North Carolina*, 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

114. CORRELATION OF CEA CONCENTRATION IN THE SERUM AND IN TUMOR TISSUES WITH ITS HISTOCHEMICAL DEMONSTRABILITY IN TISSUE SECTIONS (ABBREV)

Bagshawe, K. D., Paradinas, F. J., Charing Cross Hospital, Dept. of Medical Oncology & Histopathology, *Fulham Palace Rd., London, W6 8RF, England, United Kingdom*

OBJECTIVE: To define precisely the localization of carcinoembroyonic antigen (CEA) and other tumor markers in surgical specimens of cancers of lung, breast, stomach, colon and rectum and to correlate this information with estimations of the concentration of the same antigens measured by radioimmunoassay on serum obtained preoperatively and by extraction from fragments of the same surgical specimens.

APPROACH: There is evidence from in vivo antibody localization studies that CEA may be more widely distributed in tumors than is suggested by elevated serum levels of this marker. Confirmation of this is important if the use of cell membrane markers for antibody targeting is to be widely applicable. Information on the distribution of CEA in various tumor types and on the concentration of CEA in tumor specimens in relation to serum concentration is limited. Frozen and conventionally fixed specimens will be used for tumor marker localization by immunofluorescence and immunoperoxidase techniques. Cells in suspension will be studied and morphometric studies on the tissue preparations performed with carcinoembryonic antigen measured in serum and tissue sections by double antibody radioimmunoassay.

PROGRESS: Project started in the summer of 1979.

115. CARCINOEMBRYONIC ANTIGEN IN BREAST CANCER PATIENTS

Zamcheck, N., Boston City Hospital, Gastrointestinal Research Laboratory, *818 Harrison Ave., Boston, Massachusetts*, 02118, United States of America

This is part of a broader project. A summary of this subproject is not available.

116. LEUKOCYTE ADHERENCE INHIBITION MEASUREMENTS IN EARLY DETECTION OF CANCER

Sanner, T., Kotlar, H. K., Eker, P., Norsk Hydro's Inst. for Cancer Research, Laboratory for Occupational Cancer & Carcinogenesis, *Montebello, Oslo 3, Norway*

OBJECTIVE: To investigate the possible use of leukocyte adherence inhibition measurements in early detection of cancer and to identify groups at high risk of developing cancer.

APPROACH: The leukocyte adherence inhibition (LAI) test is based on the finding that leukocytes from sensitized persons show a reduced adherence to glass compared to leukocytes from non-sensitized persons when mixed in vitro with the relevant antigen. The published literature indicates that the LAI test possesses a high degree of specificity. Since it may take several years from the time when first cancer cells are formed to the time when a tumor is diagnosed, the possibility exists that specific cell mediated anti-tumor responses may be observed long before any clinical symptoms of the tumor appear. In the present investigation we have concentrated on breast and lung cancer. The LAI response will be measured in persons with untreated breast and lung cancer. Furthermore, measurements will be made on persons with different risk factors for developing these types of cancer, such as women with benign breast diseases, women with breast cancer in the family, smokers and persons working with asbestos.

PROGRESS: Preliminary data indicate that the number of positive LAI responses is considerabely higher in groups of women with breast cancer risk factors than in groups with a non-defined risk factor.

117. THE LEUKOCYTE ADHERENCE INHIBITION TEST - A STUDY OF THE CLINICAL USES AND MECHANISM OF THE TEST

Elliott, S. C., Iowa Methodist Medical Center, Dept. of Pediatric Education, *1200 Pleasant St., Des Moines, Iowa*, 50308, United States of America

We propose to evaluate the leukocyte adherence inhibition (LAI) test with respect to clinical usefulness in diagnosing possible breast and lung tumor patients and monitoring their progress during and after treatment. The technique used will be a modification of the tube LAI test. Procedures will be used to detect the presence of monocyte 'arming' cytophilic antibody in the serum of suspected tumor patients and individuals being treated for tumors. The monocyte chemotaxis inhibition procedure will also be used in our clinical evaluations to provide a basis for comparison of the effectiveness of the LAI test.

Attempts will be made to provide data that will clarify the mechanism of the LAI test. We propose to vary conditions of the test to determine whether different assay procedures result in changes of the cell types and mechanism of the test. We postulate that under certain assay conditions, a T-cell mediated response will be detected while other conditions will result in the detection of a monocyte-cytophilic antibody response.

An attempt will be made to purify and partially characterize the LAI-reactive material in breast and lung tumors. Purification will be attempted using differential centrifugation, gel filtration chromatography, and affinity chromatography. The LAI-reactive molecule(s) will be characterized with respect to sensitivity to a variety of physical, chemical and enzymatic agents, molecular weight, and electrophoretic and ultracentrifugation characteristics.

118. CELL-MEDIATED IMMUNITY AND ASSAY FOR BREAST CANCER

Yonemoto, R. H., Chee, D. O., Nakamura, T., City of Hope Medical Center, *1500 E. Duarte Rd., Duarte, California*, 91010, United States of America

The goal for the proposal is to develop an assay of cell-mediated immunity in breast cancer with clinical applicability, i.e., prognosis, guide to therapy and diagnosis. The rationale for the proposal is: 1) Improvement of leukocyte adherence inhibition assay, 2) utilization of highly purified TAA which should result in greater specificity in the leukocyte adherence inhibition assay (LAI), 3) parallel use of normal tissue antigen from same patient as control, 4) the use of sensitized frozen lymphocyte (allogeneic) because of easy accessibility of large quantities, access to repetitive determinations at convenience, and easy application of blocking assay, 5) in addition, basic understanding of the mode of action of LAI, i.e., cellular participation, lymphokine study, interplay of blocking factor, which will lead to an improved assay. To accomplish this goal, studies will be performed in two categories of patients.

A vertical study (patients to be entered during first two years) includes patients with benign and malignant disease, to seek comparative efficiency of LAI utilizing fresh PBL vs. frozen lymphocytes. A horizontal study (1st, 2nd and 3rd year) will evaluate patients at 1, 3 and more than 5 years post-mastectomy with no evidence of disease, as well as all patients at point of recurrent disease. All patients will undergo LAI and blocking assays at 3 month intervals as follow-up to therapy.

An improved CMI assay to monitor breast cancer patients will materialize at the end of 3 years.

BIBLIOGRAPHIC REFERENCES: Tanaka, Fumitaka, Yonemoto, Robert H., and Waldman, Stephen R. Blocking Factors in Sera of Breast Cancer Patients. Cancer, 43 (in press), 1979.

119. SIGNIFICANCE OF GP48 IN DIAGNOSIS OF BREAST CANCER

Tokes, Z. A., Dermer, G. B., Srouji, A., Imam, A., University of Southern California, School of Medicine, Dept. of Biochemistry, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

The objective of this proposal is to establish a quantitative immunoassay for gp48. The clinical significance of this gp48 immunoassay will then be assessed by monitoring patients undergoing therapy and detecting patients with malignant lesions of epithelial origin.

To achieve this, we propose to biosynthetically label gp48 with 3H-carbohydrate or 14C-carbohydrate precursors using any of the systems available to us, with the main emphasis on using human breast cancer surgical specimens maintained in organ culture. In addition, we will examine human breast tumor lines propagated in athymic nude mice and cell culture systems of established malignant human breast epithelial cell lines as potential sources for labelled gp48. The biosynthetically labelled gp48 will be used as a tracer to isolate mg quantities of this component from any one of these three systems or from the sera of patients with demonstrated elevation of glycoproteins in the alpha-2-beta electrophoretic region. Purification procedures will utilize, in addition to the standard biochemical steps, lectin affinity chromatography, preparative electrophoresis, immunoaffinity chromatography and ion-exchange chromatography. The purified glycoprotein will be used for the production of immune antisera. After appropriate adsorptions, the specific antisera will be utilized to establish a quantitative immunoassay using a non-radioactive immunodiagnostic procedure with rate nephelometry instrumentation, or radioimmunoassay using 125I-labelled gp48.

BIBLIOGRAPHIC REFERENCES: Silverman, L.M., Dermer, G.B., and Tokes, Z.A. (1979) Serum glycoprotein electrophoresis. Compendium of Assays for Immunodiagnosis of Human Cancer (Ed. R.L. Herberman). Elsevier North Holland, Inc. p. 93-96. Dermer, G.B., and Tokes, Z.A. (1979) Glycoprotein release from cell surfaces of intact human adenocarcinomas. J. Supramolecular Struct. Suppl. 3, 189 (467).

120. IMMUNODIAGNOSIS, IMMUNOTHERAPY AND IMMUNOLOGICAL MONITORING IN HUMAN CANCER

Bonnard, G. D., Navarro, N., Herberman, R. B., Ortaldo, J. R., Pandolfi, F., Kedar, E., Gerson, J. M., Lang, N. P., Yasaka, K., Fagnani, R., Alvarez, J., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Laboratory of Immunodiagnosis, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

We studied human T cell activation and regulation in the system of continued cultured T cells that responded to a mitogenic factor or T cell growth factor. These were from supernates of phytohemagglutinin-stimulated lymphocytes. Concanavalin A, alloantigens, and soluble antigens were also studied for their ability to induce factor production. The cultured T cells maintained cytotoxicity after mixed lymphocyte culture and mixed lymphocyte tumor interaction CTC maintained other functions as well. Plans are to derive T cells reactive specifically with tumor-associated antigens in acute myeloblastic leukemia, breast cancer and lung cancer.

BIBLIOGRAPHIC REFERENCES: Kay, H.D., Bonnard, G.D., and Herberman, R.B.: Evaluation of the role of IgG antibodies in human natural cell-mediated cytotoxicity against the myeloid cell line K562. J. Immunol. 122: 675-685, 1979. Metzgar, R.S., Bertoglio, J., Anderson, J.K., Bonnard, G.D., and Ruscetti, F.W.: Detection of of HLA-DDw (Ia-like) antigens on human T lymphocytes grown in tissue culture. J. Immunol. 122: 949-953, 1979.

121. IMMUNODIAGNOSTIC MARKERS FOR BREAST CARCINOMA

Chawla, R. K., Emory University, School of Medicine, Dept. of Medicine, *1364 Clifton Rd. N.E., Atlanta, Georgia*, 30322, United States of America

OBJECTIVES: Prepare a supply of pure EDC1, pure IATI (inter-alpha trypsin inhibitor), and high titer antiserum to EDC1; the EDC1 method shall be standardized. Utilize CIEP to measure the plasma and urine levels of EDCU and LATI in normal women, those with benign diseases, and those with breast carcinoma. Perform plasma/urine EDC1 measurement preoperatively on patients with a localized breast mass and follow those patients postoperatively in consultation with and approved by the project officer.

122. PREDICTION OF RECURRENCE RATES AFTER MASTECTOMY

Thomas, B. S., Imperial Cancer Research Fund, Clinical Endocrinology Laboratory, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

Over 600 specimens of blood and urine have been obtained from women with Stage 1 or 2 breast cancer (see ICRF Scientific Report 1978 -report 29). Urinary steroid profiles have been measured in 180 cases. There is a highly significant relationship between the amounts of androsterone and aetiocholanolone excreted in the urine and recurrence rates after mastectomy. Patients who excrete large amounts of these steroids have an excellent prognosis. The relationship between steroid excretion and stage appears to be very complex. Urinary steroids are most useful as discriminating agents in patients with 1-3 involved lymph nodes.

123. IMMUNE ASSAYS FOR ENZYMES AND ISOZYMES IN CANCER

Shaper, J. H., Johns Hopkins University, School of Medicine, Dept. of Oncology, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

OBJECTIVES: Evaluate the immunodiagnostic significance of serum levels of UDP-galactosyltransferase in human breast and ovarian carcinoma. Specifically: develop a sensitive and highly specific radioimmunoassay for human serum galactosyltransferase, systematically examining the efficacy of antiserum produced from bovine milk, normal human serum,and human ascitic fluid; determine if a cancer-associated isoenzyme of galactosyltransferase, chemically similar to the isoenzyme reported in serum, is present in human ascitic fluid; assess the immunological cross-reactivity or relatedness of galactosyltransferase isolated from the three sources listed above; and once the radioimmunoassay has been developed, conduct, after consultation with the Project Officer, a clinical study correlating serum UDP-galactosyltransferase levels with tumor burden, disease state, and response to therapy.

124. IMMUNOLOGIC RESPONSE OF REGIONAL LYMPH NODE CELLS

Cunningham Rundles, S., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

The involvement of regional lymph nodes with tumor may be the most important prognostic indicator in breast cancer. However, little work has been done in investigating the immunologic aspects of the regional lymph node cells (RLNC) in this disease. A histopathologic correlation has been suggested between prognosis and sinus histiocytosis which may be indicative of a local immune response. Other studies indicate an antigenic stimulation of the RLNC closest to the tumor. Most in vitro studies have stressed the immunologic competence of RLNC. However, little has been done on cell-mediated immune responses specific for breast cancer associated antigens. Recent work demonstrates inhibition of leukocyte migration with RLNC that was greater than with peripheral blood cells using a crude breast cancer homogenate antigen. These studies suggest the need to test the in vitro reactivity of RLNC in order to ascertain its usefulness in predicting recurrence of breast cancer. This project would be designed for that purpose.

125. BIOCHEMICAL MARKERS IN CANCER

Malkin, A., Kellen, J. A., Sunnybrook Hospital Medical Centre, Dept. of Clinical Biochemistry, *2075 Bayview Ave., Toronto, Ontario*, M4M 3M5, Canada

OBJECTIVE: The objective of this study is to identify optimal biochemical marker combinations in various solid tumors, which would enable us to stratify cancer patients into more homogenous prognostic groups for clinical trials, facilitate the monitoring of treatment and lead to more individualized therapy. The following markers are currently under investigation: Carcinoembryonic antigen, alpha-fetoprotein, placenta-like alkaline phosphatase, chorionic gonadotropin and the acute phase proteins, C-reactive proteins, acid glycoprotein and alpha-1 anti-trypsin. Furthermore, the prognostic value of the trend as expressed in at least four consecutive CEA determinations during a period of at least 6 months is being analyzed in patients with cancer of the breast.

PROGRESS: Our results so far indicate that single markers lack both specificity and sensitivity; different marker combinations are required for different tumors. In primary breast cancer, post-operative patients with elevated CEA levels are more prone to develop recurrent disease; this appears to be independent of nodal status and stage.

126. THE INTERRELATIONSHIP OF TUMOR BEHAVIOR AND HOST IMMUNE COMPETENCE IN THE CANCER PATIENT

Hughes, L. E., Hillyard, J. W., University of Wales, Welsh National School of Medicine, Dept. of Surgery, *Heath Park, Cardiff CF4 4XN, Wales, United Kingdom*

OBJECTIVE: To determine whether general immune competence is depressed in patients with malignant disease, and whether there is any correlation, in the individual case, between the degree of immune competence and early tumor recurrence or prognosis. Sequential follow-up tests are being used to determine whether any pattern of results correlates with subsequent tumor behavior.

APPROACH: The tests of immune competence being used are total WBC and absolute and relative lymphocyte counts, serum immunoglobulin levels (IgG, IgA, IgM and IgE), lymphocyte transformation with PHA, Mantoux and DNCB skin tests. All patients are studied before any form of treatment is given. The first follow-up test is at one month after treatment and subsequent tests are at three months and then at three-month intervals for 2 years, after which the tests are yearly.

PROGRESS: Two hundred patients with breast cancer and 120 patients with stomach and colorectal cancer have now been followed up for 2 years and the results are being analyzed. Impairment of immune response has been demonstrated in all groups of cancer patients - a notable exception being those with locally advanced breast cancer. As indicators of prognosis, these tests of immune competence have so far been no more accurate than clinical staging.

127. IMMUNOLOGICAL EVALUATION OF PATIENTS WITH RAPIDLY PROGRESSING BREAST CANCER

Mourali, N., Epstein, R., Tabbane, F., Belhassen, S., El Meddeb, A., Salah Azaiz Inst., Laboratory of Immunology, *Blvd. du 9 Avril, Bab Saadoun, Tunis, Tunisia*

OBJECTIVE: To determine the general immunological status of patients with rapidly progressing breast cancer (PEV) using a battery of in vitro and in vivo immunological assays designed to measure the immune competency of the host. It is hoped that these procedures can be shown to be of value clinically to monitor the patient's progress during a treatment protocol consisting of combination chemotherapy and either radiotherapy or surgery.

METHODS: PEV positive patients with no evidence of clinical metastasis will undergo 18 cycles of chemotherapy. After the third cycle they will be randomized between radiotherapy and surgery. At monthly intervals commencing before any treatment is initiated, peripheral blood samples will be obtained from each patient. Lymphocytes will be purified and nonspecific reactivity to PHA, ConA and PWM will be determined using a tritiated thymidine uptake assay. Crude antigen will be prepared from autologous tumor samples and patients' reactivity toward their tumor will be analyzed by thymidine incorporation. Other in vitro CMI assays to be employed will be MLC, migration inhibition, PHA induced cytotoxicity, antibody dependent cellular cytotoxocity and a new assay denoted as SINEC (specifically induced nonspecifically expressed cytotoxicity). In SINEC lymphocytes are specifically activated by tumor antigen and will nonspecifically express their cytotoxic capability by lysing unrelated targets. Additional immune parameters to be used will include skin testing and T cell rosetting.

128. LABORATORY ASSESSMENT OF PROGNOSIS IN CARCINOMA OF THE BREAST AND LUNG

McCulloch, P. B., Dent, P. B., Pater, J., McMaster University, Hamilton Cancer Clinic, *711 Concession St., Hamilton, Ontario*, L8S 4J9, Canada

OBJECTIVE: Elevated levels of a number of non-specific but malignancy-associated serum factors have been reported in breast and lung cancer patients. Disease-free postoperative stage II breast cancer patients are followed at six week intervals for one year, in an attempt to forecast relapse before it becomes clinically evident since intervention at that juncture might prevent relapse and thus prolong life. In oat cell bronchogenic carcinoma complete remissions are frequently achieved with combination chemotherapy and the completeness of such remissions can be judged by sequential studies of similar serum factors.

APPROACH: Patients with stage II breast cancer or patients with oat cell carcinoma rendered disease free by chemotherapy and radiotherapy are followed at six to eight week intervals with estimations of CEA, ferritin C reactive protein, C1q binding assay for immune complexes.

PROGRESS: In breast cancer, 104 disease-free patients have been followed with the above parameters. Twenty have subsequently relapsed. The serum parameters become abnormal at an average of 6-12 weeks before the relapse becomes clinically evident in 50-80 percent of patients.

129. IMMUNOLOGICAL STATUS OF BREAST CANCER

Desplaces, A., Brunet, M., Berlie, J. G., Gest, J., Bourguignat, A., Oglobine, J., DeRicqles, D., Saracino, R. T., Centre Rene Huguenin Contre Cancer, *5 Rue Gaston Latouche, 92211 St. Cloud, France*

OBJECTIVE: The aim of the present work is to utilize examinations performed for several years in order to determine the immunological status of the breast cancer patients.

APPROACH: This research will: 1. Study the homogeneity of test responses and dosages with respect to the elaboration of standards. 2. Reveal an eventual relationship between the patient's profile, disease and pre-treatment examinations. 3. Evaluate these results in course of time in correlation with therapeutic methods and cancer history.

130. STUDY OF TRANSFORMED MAMMARY EPITHELIAL CELLS IN VITRO

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Isolate and identify tumor-related antigens from neoplastic human mammary epithelial cells and develop assays that will be useful in clinical diagnosis, prognosis, and evaluation of therapeutic measures. Determine whether tumor-related antigens from different patients with breast cancer possess common antigenic determinants, and whether these are related to antigenic determinants in neoplastic cells of other organs. Identify structural features that are similar or identical among tumor-related antigens.

131. IMMUNOLOGICAL ASPECTS OF CANCER PROGNOSIS

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In this project, immunological reactivity of cancer patients will be studied before treatment and during chemotherapy and immunotherapy. The objective of the study will be to establish the relationship between immunocompetence and prognosis, and to accurately evaluate the immunological effects of chemotherapy and immunotherapy. The least immunosuppressive chemotherapy and the most immunopotentiating immunotherapy will be sought. The immunological tests to be evaluated will include skin tests with recall antigens, a lymphokine skin test, and a variety of cell-mediated immunity studies in vitro, including the following: tests of macrophage function including 14C glucosamine incorporation, phagocytosis and macrophage cytotoxicity, lymphocyte cytotoxicity induced by allogeneic stimulation, and antibody-dependent cell-mediated cytotoxicity. The disease categories to be studied will include melanoma stage III and IV, breast cancer stage IV, lung cancer stages I-IV, and leukemia. Immunotherapies to be studied include BCG, C. parvum and MER. The potential benefit will be improved prognostication for the cancer patient and the selection of better therapies.

132. CELL SURFACE MODULATION IN MAMMARY NEOPLASIA

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Antigenic cell surface modulation associated with malignant transformation will be investigated in order to obtain a clear distinction between the normal, preneoplastic and neoplastic mammary epithelial cells. Initial studies on the cell surface components of normal and tumor mammary epithelial cells have established that the normal mammary cell surface membrane has an additional component which can be radiolabeled with either fucose or iodine. Further research will be aimed towards characterization of the antigenic structure of normal and tumor cell surfaces. Xenogeneic antibodies have been prepared to normal mammary epithelial cell-specific antigens and to virus-associated antigens. Syngeneic antibodies to mammary tumors (from tumor-bearing animals) have also been isolated. After appropriate absorptions, these antibodies will be used in immunofluorescence studies to determine the presence and location of the respective antigens and the interrelationship with other normal cell surface antigens (i.e., H-2, Thy. 1). In addition, these specific antibodies to normal and tumor-associated antigens will be utilized in radioimmunoprecipitation experiments followed by gel electrophoresis to characterize the respective antigens. Both the qualitative and quantitative differences in cell surface structure of normal and tumor mammary epithelial cells will be defined. Preneoplastic (HAN) epithelial cells will be compared to both normal and tumor mammary epithelial cells in order to assess early events in cell surface modulation accompanying the preneoplastic state.

133. THERAPY EFFECTS ON TUMOR KINETICS AND IMMUNE PARAMETERS

Fisher, B., Gunduz, N., Wolmark, N., Ratajczak, H., University of Pittsburgh, School of Medicine, Dept. of Surgery, *3550 Terrace St., Pittsburgh, Pennsylvania,* 15261, United States of America

Investigations carried out in this laboratory have been directed toward evaluating the use of combined modality treatments, i.e., immunochemotherapy, on the growth of a primary tumor and metastases. It was observed that when C. parvum (CP) was administered i.p. asynchronously in combination with cyclophosphamide (CY) at weekly intervals to C3HeB mice bearing an established growing C3H mammary adenocarcinoma, tumor growth inhibition was achieved which was greater than that resulting from either agent alone. In additional investigations, other chemotherapeutic and non-specific stimulating agents were substituted for or added to the CY, CP combination. None, when substituted, produced results equal to that combination, nor did their addition improve the results. We have attempted to identify host responses resulting from the therapy which might be responsible for the overall effectiveness of the combination. None of the investigations provided clear evidence implicating any of the host factors in the general success of treatment. Of particular interest has been the observation that in all experiments employing this combination of therapy, the effect on tumor growth varied from mouse to mouse despite the fact that tumors in any one study were from the same inoculum and were in syngeneic hosts. Whether this divergence was the result of disparate host modulation or differences in tumor characteristics was speculative. The present investigations with two C3H mammary tumors in the same host indicate that the tumors rather than the host are responsible for the observed variation in treatment effectiveness. They suggest that each inoculum contains a heterogeneous tumor cell population so that aliquots of the suspension upon transfer produce, by chance, clones giving rise to tumors having variable susceptability to the therapy. Preliminary investigations evaluating tumor cell kinetics have shown that the cytokinetics of those tumors responding best to treatment differ from those responding least. Investigations during the coming year will continue to assess tumor and host factors in responders and non-responders to chemo-immunotherapy.

134. SEQUENTIAL IMMUNOLOGIC PROFILE OF CANCER PATIENTS UNDERGOING SURGERY AND ADJUVANT CHEMOTHERAPY

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OBJECTIVE: Sequential monitoring of the immunologic profile of cancer patients undergoing radical surgery and adjuvant chemotherapy for treatment of the following neoplasms: melanoma, gastric carcinoma, colorectal carcinoma, breast carcinoma.

APPROACH: Sequential determinations of the immunologic profile are carried out in neoplastic patients of both sexes undergoing radical surgery for the removal of localized primary tumor of one of the previously described histologic types. The following immunologic tests representative of non-tumor-specific host defense mechanisms are performed preoperatively (twice, on 2 different days) and postoperatively at monthly intervals, before chemotherapy cycles: a) in vivo delayed hypersensitivity response to skin antigens (DNCB, Candida, Trichophyton, tuberculin, streptokinase-streptodornase); b) total lymphocyte count in peripheral blood; c) T-lymphocyte count; d) lymphocyte blastogenic response to phytohemagglutinin (PHA, optimal and suboptimal doses); e) plasma levels of IgG, IgA, IgM, C3c, C4 and Factor B.

Patients are followed up clinically every month by means of physical examination, routine laboratory tests, X-rays and scintigrams of target organs at 6-month intervals.

PROGRESS: The project was activated 2 years ago. To date evaluation has been carried out in 12 melanomas, 12 breast carcinomas, 15 gastric carcinomas, and 11 colorectal carcinomas.

135. SPECIFIC IMMUNITY AND PROGNOSIS IN BREAST CANCER

Black, M. M., Zachrau, R. E., Leis, H. P., Isac, M. J., New York Medical College, Westchester Campus, School of Medicine, Dept. of Pathology, *Valhalla, New York,* 10595, United States of America

Individual cancer patients were tested repetitively, at increasing postoperative intervals by a leukocyte migration test (LMT) and a skin window (SW) procedure. One quarter of 48 patients demonstrated LMT reactivity 1-8, 9-14 and 15-24 months post-operatively while one-fifth of the patients were minimally responsive during each of these intervals. Among 21 patients showing minimal reactivity to autologous breast cancer 1-8 months postoperatively, approximately half were reactive 9-14 and/or 15-24 months postoperatively. CMI to autologous breast cancer 9-24 months postoperatively was prognostically favorable regardless of the reactivity 1-8 months postoperatively.

The phenomenon of spontaneous variations in CMI to autologous breast cancer suggests the possibility of experimentally maintaining or inducing such reactivity. Spontaneous variations in LMT reactivity to autologous breast cancer also provide a device for evaluating the specificity of such reactivity by simultaneously testing other targets. Among individual patients, tested repetitively 9-50 months postoperatively, reactivity to autologous breast cancer was correlated with reactivity to gp 55 of R III MuMTV and to its (gp 55) glycopeptide fraction. No such correlation was found with fetuin, its glycopeptide, benign breast lesions or colon carcinoma.

Horizontal studies of simultaneous LMT reactivity to autologous breast cancer and selected targets provide important insights into the biological significance and specificity of such reactivity. Such information is pertinent to the development of immunotherapy and immunoprophylaxis and to the choice of patients for adjuvant chemotherapy.

136. CONTROL OF BREAST CANCER BY SERUM GROWTH FACTORS

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The interaction of insulin and epidermal growth factor (EGF) with cultured human breast cancer cells has been investigated. All cell lines examined have specific high affinity receptors for insulin and EGF. However, only certain of these cell lines have retained the ability to respond biologically to these hormones. In these lines both insulin and EGF in physiologic concentrations stimulate protein, RNA, and DNA synthesis in a sequential fashion. Cell proliferation is also significantly augmented by these factors although the effects at optimal concentrations are not additive suggesting similar pathways of action. These cell lines are currently being used to study the biochemical steps of the mechanisms of insulin and EGF action distal to receptor binding.

137. CANCER DIAGNOSIS AND CANCER PATIENT MANAGEMENT

Chu, T. M., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

OBJECTIVE: Evaluate plasma carcinoembryonic antigen serially in 600 patients who have gastrointestinal or other intra-abdominal malignancy, cancer of the lung or breast, and neuroblastoma by determining a baseline value on all new patients who fit into one of these categories, evaluating CEA levels four and fourteen days after surgery and additional testing done at 30 and 60 days and every three months thereafter. For radiation therapy patients, testing will occur at two-week intervals during the therapy, and at monthly intervals thereafter. Chemotherapy patients will be tested weekly for ten weeks and then monthly. Controlled plasma specimens will be assayed in each CEA test.

138. HISTOLOGICAL, CYTOLOGICAL AND HISTOCHEMICAL ALTERATIONS IN HUMAN MAMMARY CANCER

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The summary for this project is under entry no. 80.

D. KINETICS, HISTOPATHOLOGY, AND STAGING IN DIAGNOSIS AND PROGNOSIS

139. PATHOLOGY OF BREAST TUMORS IN THE GUERNSEY PROSPECTIVE TRIAL

Millis, R., Hayward, J. L., Bulbrook, R. D., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

Review of breast cancers occurring in women who took part in the Guernsey prospective trial continues. Histological sections from all tumors developing in these women are examined and features which may be of prognostic significance evaluated. Particular note is made of the degree of inflammatory reaction, consisting mainly of lymphocytes and plasma cells, around and within the tumor, as preliminary studies have indicated that the degree of cellular reaction may be correlated with the levels of urinary aetiocholanolone in these women.

140. EARLY BREAST CANCER - PATHOLOGY AND PROGNOSIS OF BREAST CANCER DEVELOPING IN PATIENTS TAKING ORAL CONTRACEPTIVES

Hayward, J. L., Millis, R., Matthews, P. N., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

An analysis has been carried out on all patients with breast cancer who have taken oral contraceptives at any time in the past. Clinical and histological features and prognosis have been compared with those in matched controls. A significantly higher number of the control patients had larger tumors and more extensive axillary node involvement than was found in the study group. Furthermore, a significantly greater number of patients in the study group had close relatives (mother or sister) who had had breast cancer than in the control group but the difference was not significant. These findings tended to reinforce those which had been reported in an earlier study on patients who had been taking the contraceptive pill during the year prior to diagnosis.

141. STUDY OF MORPHOLOGY OF NORMAL/ ABNORMAL MAMMARY TISSUE

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OBJECTIVES: Test the general hypothesis that transmission or scanning electron microscopy can be useful for the early diagnosis of mammary neoplasia and preneoplastic or premalignant conditions. Differentiate normal (aging, senile) or benign cellular alterations from preneoplastic and neoplastic lesions of the human mammary gland. Describe, quantitate, and compare certain morphological and functional characteristics of normal, hyperplastic, and carcinomatous human and mouse mammary glands in vivo and in vitro. From this data we will determine whether some or any of the parameters enable us to predictably recognize patterns diagnostic of carcinoma, of premalignant lesions, or of tissue responsiveness to therapeutic procedures.

142. DIAGNOSTIC AND AETIOLOGICAL IMPLICATIONS OF MAMMOGRAPHIC CALCIFICATIONS IN BREAST DISEASE

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The presence of multiple punctate calcification in the breast and its association with breast carcinoma has been reported by many investigators. In the course of clinical mammography during the past several years we have detected calcifications in numerous cases of carcinoma of the breast and, in many of these, the presence of calcification on the mammogram in the absence of a palpable mass was the only sign of carcinoma. We have obtained genetic, epidemiological, pathological, and radiological information on 2,338 women who were radiographed for clinical indications of breast disease at the Toronto Western Hospital from 1968 to 1973. Biopsies or mastectomies were done for surgical or radiological suspicion of malignancy in these women. The biopsies indicated that 354 women had breast

cancer, 1,713 had benign breast disease, and 272 had no apparent breast disease. We are studying the genetic, epidemiological, pathological, and radiological factors in those diagnosed as having breast cancer, those who had benign breast disease, and those without apparent breast disease. From the availabie pathological and radiological information on these women, we are also determining if a certain pattern of calcification correlates with (1) the presence of breast cancer, (2) the type of breast cancer, and (3) the type and degree of fibrocystic disease if carcinoma is not diagnosed pathologically.

143. SMALL CELL IN SITU LESIONS OF THE FEMALE BREAST

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Small cell lesions of the female breast (lobular carcinoma in situ) are found in some 8% of breast biopsies taken for benign conditions. The long-term behavior of the lesion still awaits elucidation. Current evidence would suggest that some 20% of patients with this lesion will develop an invasive carcinoma in either the ipsilateral or the contralateral breast when followed over a 20-year period. Most of these invasive tumors will appear within 15 years after detection of the initial small cell lesion. What remains to be established is whether any relationship exists between the dimension of the original small cell lesion and the incidence of subsequent invasive carcinoma. Although our own series includes some 100 patients, and although the number is being augmented, resolution of this problem requires a much larger number, probably thousands. This will require a collaborative effort of national or international dimensions. Such an effort will require a major investment of time and money, but it will provide both prognostic and demographic, as well as, possibly, aetiological data that would adequately justify the expense.

144. QUANTITATIVE STUDIES OF HUMAN BREAST PATHOLOGY

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Our purpose is to quantify mammary epithelial lesions in large numbers of biopsy size samples of human breast tissue using our own histological grading methods and to correlate the findings with risk as determined by other histological methods, by mammography, and by the actual appearance of cancers in the patients studied.

Differential counts of different kinds of lesions are determined, and these are scored according to severity and amount of atypia, which can be further related to area of tissue on the slides.

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145. CELL PROLIFERATION AND LOSS KINETICS IN HUMAN TUMORS AND LIMITING NORMAL TISSUES

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OBJECTIVE: The measurement of cell proliferation and loss in human breast tumors in situ before and during treatment.

APPROACH: Iso-transplanted murine mammary carcinoma will be used to develop methods of measuring the cell kinetics of tumors in situ. The results of such methods will be compared with the cell kinetics parameters of the model tumors obtained by conventional techniques involving isotope tracer administration and sacrifice of the animal. Measurements will then be made, with the methods developed, of human breast tumors in situ. The techniques to be used are: 1) Serial sampling to study mitotic accumulation after an injection of vincristine. This technique will be used to analyze both untreated and irradiated tumors. When the results can be interpreted in terms of the tumor cell kinetics, serial biopsies from patients undergoing vincristine therapy will be analyzed. 2) Injection and external counting of radioactive iododeoxyuridine (IUdR). Techniques will be developed for local injection of this nucleotide into or around the tumor. IUdR will then be administered locally to breast cancer patients and the tumor will be scanned regularly with a gamma camera. We hope to estimate the proportion of actively proliferating cells and their location in the tumor. Loss of cells from the tumor will also be estimated.

PROGRESS: This is a newly funded project.

146. KINETICS OF CELLULAR PROLIFERATION

Young, R. C., Chabner, B. A., Myers, C., Newburger, A., McGuire, W., Schackney, S., Ozols, R., Fisher, R. I., Locker, G., Doroshow, J., Smyth, J., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Cellular Kinetics Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The primary goal of the Cellular Kinetics Section is to achieve a better understanding of the kinetic behavior of normal and tumorous tissues and to use such information to design optimal forms of chemotherapy. Toward this end both animal studies and studies of patients have been undertaken.

This year, alterations in DNA synthesis induced by chemotherapy in normal and tumorous murine tissues have been completed and results have been published. Cellular kinetics studies in an ovarian carcinoma murine tumor model have been completed and accepted for publication this year. Pharmacokinetics of intraperitoneal administration of methotrexate and adriamycin have been related to cellular kinetics, tissue penetration and systemic toxicity for the first time. Other animal studies include: The kinetics effects of tamoxifen followed by estrogen, tamoxifen or estrogen alone have been studied in DMBA induced breast cancer in Sprague-Dawley rats. The tumors are studied by autoradiography, TdR incorporation, and flow cytometry. No evidence of recruitment or synchronization with estrogen, following tamoxifen occurred at 1,2, or 3 days post-therapy. This experiment is being repeated, using a different time schedule, to look for evidence of recruitment following hormonal therapy.

Studies are proceeding with cultured murine melanomas (Cloudman CCL-53, IA and Mel) and human melanomas (FCC-1 and HM-1) to look for melatonin-receptors and responsivity to MSH as measured by increased tyrosinase production.

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147. THERAPY EFFECTS ON TUMOR KINETICS AND IMMUNE PARAMETERS

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The summary for this project is under entry no. 133.

148. MECHANISMS OF GROWTH, METASTASIS AND REGRESSION OF HUMAN BREAST CANCER IN NUDE MICE

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Solid mammary tumors are induced in nude mice by s.c. injections of the human breast cancer cell lines MCF-7 or ZR-75. Tumor induction is estrogen dependent, and prolactin (but not progesterone) appears to also have a stimulatory effect. The high frequency of lung, spleen and liver metastases makes this system particularly useful in the ongoing study on the mechanism of basement membrane invasiveness by tumor cells and the role of hormone both in vivo and in vitro in this process. Tumor growth proceeds even when the tumor host is ovariectomized but tumors regress when the host is treated with antiestrogens. This raised the possibility that these tumor cells continue to be estrogen dependent but have the potential of making their own hormones. We are investigating the possibility of a paraendocrine activity by these cells and their solid tumors and are in the process of designing experiments on combined endo-

crine and chemotherapeutic protocols that could induce an appropriate and most effective tumor regression.

149. REGIONAL DIFFERENCES IN GROWTH OF BREAST TUMORS OF SPONTANEOUS ORIGIN IN THE RAT

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OBJECTIVES: To study the mechanism of regression of the Sp4 tumor inoculated in the right anterosuperior region of the thorax.

APPROACH: To study the possible role of hormones and the immune system.

PROGRESS: Studies which we performed in the University of Nottingham, England, in 1978 indicate that spontaneous mammary adenocarcinoma in Wistar/Not. rats (Sp4), by intramammary injection, demonstrate different growth characteristics according to the site of the intramammary injection. The adenocarcinoma grows continually, leading to death, if injected in the right mamillothoracicoabdominal region; it regresses spontaneously if injected in the superior mamilla of the same side. We are currently reproducing these results in our Department with the same congenital strain of Wistar/Not. provided from England and maintained by crossing among offspring of the same litter.

150. ADVANCED BREAST CANCER - A STUDY OF ELASTOSIS IN PRIMARY TUMORS IN RELATION TO RECURRENCE RATE AND RESPONSE TO ENDOCRINE THERAPY

Millis, R., Rubens, R. D., King, R. J., Masters, J. R., Minton, M. J., Hayward, J. L., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

The summary for this project is under entry no. 69.

151. THE GRADING OF MALIGNANCY OF HUMAN BREAST CANCER IN FINE NEEDLE ASPIRATES

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The summary for this project is under entry no. 72.

152. HISTOLOGICAL, CYTOLOGICAL AND HISTOCHEMICAL ALTERATIONS IN HUMAN MAMMARY CANCER

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The summary for this project is under entry no. 80.

153. CLINICAL CANCER RESEARCH CENTER

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The summary for this project is under entry no. 78.

154. STUDY OF STEROID SULFATION AND ESTROGEN BINDING

Dao, T. L., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

The summary for this project is under entry no. 94.

155. IMMUNOPHARMACOLOGIC CONSEQUENCES OF TUMOR HETEROGENEITY

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Five tumor subpopulations have been isolated from a single strain BALB/cfC3H mouse mammary tumor. These subpopulations have been found to differ in regard to morphology, growth characteristics, karyotype, expression of unique and virus-associated tumor antigens, sensitivity to cytotoxic drugs, and sensitivity to x-irradiation. Four of the subpopulations are stable, whereas the fifth is capable of giving rise to new, tumorigenic variants. The immunopharmacologic consequences of tumor heterogeneity are being studied by observing the growth characteristics, immunogenicity, and drug sensitivity of selected mixtures of the subpopulations growing in vivo and in vitro. So far, the growth of individual subpopulations has been shown to be influenced by the presence of another subpopulation. Immunologic responses seem to be involved in these interactions, as well as non-cellular mediator which is produced by two of the subpopulations and released into culture medium.

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156. ADENOMA IN BREAST NEOPLASIA

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Numerous authors have proposed 'indices' of various parameters to evaluate the immune response of the host in cancer. Hamlin in 1968 devised the 'index of patient survival time'. Fegis, et al., in 1977, using such parameters as lymphocytic infiltration of peripheral tumor, histiocytosis of the medullary sinus, and follicular hyperplasia, devised the 'survival index'. Wenebo et al. in 1979 devised the 'relapse index' based on metastatic tumoral infiltration of lymph nodes, histopathological tumor type, DNCB response and lymphocyte response. Humphrey, et al., in 1974, used various serological tests for the early diagnosis of breast cancer. These authors concluded that it is preferable to perform histopathological examination of breast nodes or of axillary nodes where there are metastases.

To evaluate the possibility of diagnosis of breast carcinoma by immunopathologic study of axillar lymph nodes without metastases, we are studying axillary lymph nodes in 20 women undergoing surgery for breast cancer and axillary lymph nodes from 20 women who have died of non-neoplastic cause. The lymph nodes are prepared in the usual fashion in paraffin block and stained by HE or by a modification of the Unna Pappenheim method (staining of pyroninophilic cells). Three consecutive photographic slides are made of each microscopic slide of the para-cortical region. The pyroninophilic cells will be counted by projecting the photographic slides on a grided screen.

The following cells will be identified: Macrophage system - lymphoreticular, histiocytic and macrophage cells; lymphocytes - clear and pyroninophilic cytoplasm; lymphoblasts - clear and pyroninophilic cytoplasm. Slides stained by HE will be studied for the presence of histiocytes, volume of lymphoid follicles and size of the follicular germination center. Results will be grouped according to presence of metastases in cases with carcinoma, and cause of death and presence of breast lesions in non-carcinoma cases.

157. SIGNIFICANCE OF CELLULAR RETINOIC ACID BINDING PROTEIN, ORNITHINE DECARBOXYLASE AND POLYAMINES AS POSSIBLE MARKERS IN PRENEOPLASIA

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OBJECTIVE: Retinol (vitamin A), retinoic acid and their synthetic analogs, commonly known as retinoids, are highly promising agents which are able to prevent or induce reversal of cell transformation. At this time, the mechanism of action by which retinoids exert their effect is not yet known. It has been proposed that retinoids behave like steroids, since specific cellular binding proteins for retinoic acid (cRABP) were found in several developing, as well as fast dividing and tumorous, tissues. cRABP was, therefore, suggested to be used as a biochemical marker for early detection of cancer.

APPROACH: During the last two years significant progress was made in determining, by various methods, the specific binding protein for retinoic acid. This method allows quantitative determination of the specific cellular binding protein for retinoic acid and is very accurate and highly sensitive.

PROGRESS: Results from our laboratory show that specific binding for retinoic acids occurs not only in cancerous tissue of human mammary tumors, but also in preneoplastic stages (simple and proliferative dysplasia). Only very little activity of ornithine decarboxylase could be found in human mammary tissue which does not allow use of this enzyme as a biological tumor marker.

E. DETECTION OF DISTAL METASTASES FROM BREAST CANCER

158. HYDROXYPROLINE IN BONE METASTASIS FROM BREAST CANCER

Palmieri, G. M., Neely, C. L., Niell, H. B., Wilson, R. J., McDonald, M., Seyer, J. M., University of Tennessee, Center for the Health Sciences, School of Medicine, Dept. of Medicine, *62 S. Dunlap St., Memphis, Tennessee*, 38103, United States of America

Bone metastasis occurs in 49% of patients with cancer of the breast. Although the diagnosis is currently made by x-rays and scintiscanning, there are no accurate indicators for the evaluation of the early response to therapy. Since bone matrix is the largest store of collagen, the invasion of bone by metastatic cancer is accompanied by an elevated excretion of hydroxyproline (HYPRO) in urine. HYPRO is excreted as dialyzable and non-dialyzable forms; the former represents breakdown of mature collagen, the latter is an index of synthesis of new collagen. It is therefore likely that serial determinations of dialyzable and non-dialyzable HYPRO can be an important tool in the evaluation of therapeutic response in patients with cancer of the breast with skeletal metastasis. In continuation of studies conducted we proposed to determine in patients with cancer of the breast: 1) If the highly simplified procedure of HYPRO/creatinine ratio in morning urine ('SPOT-HYPRO') currently used in our laboratories, is an accurate index of the presence and response to therapy of bone metastasis. 2) If the elevation of non-dialyzable HYPRO excretion, observed 24-48 hrs after chemotherapy is an index of immediate response to therapy and if the test has prognostic value for long-term treatment. 3) If there is correlation between the metastasis/normal bone ratio of densitometry in bone scans with the urinary excretion of HYPRO, as preliminary data from our laboratories appear to indicate. 4) The validity of HYPRO measurements as an index of bone metastasis by determining the glucosylgalactosylhydroxylysine/galactosylhydroxylysine ratio in urine. This test differentiates the tissue of origin of the increased collagen turnover as bone or soft tissues.

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159. BIOCHEMICAL CHANGES IN THE DEVELOPMENT OF BREAST CANCER

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The levels of haptoglobin, sialic acid and fucose are investigated in the sera of patients with malignant and benign tumors of the breast and in those of healthy subjects. The determination of these biochemical parameters is carried out according to standard methods. Fucose is determined as described by Dische and Shetler, sialic acid according to Seiter and Gerstenfeld, and haptoglobin by using the peroxidase activity as indicated by Owen.

Preliminary results indicate that the levels of haptoglobin, sialic acid and fucose increase according to the development of malignancy. The increase of these parameters as determined at different time intervals within a period of 1.5 years after the surgical removal of the primary tumor preceded by about two months the radiological diagnosis of metastases. Therefore, these simple biochemical determinations appear to permit early detection of metastases and the bilateral extension of cancer of the breast.

160. LYMPHATIC METASTASIS OF TUMORS

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OBJECTIVE: The objective of this project is to elucidate the mechanisms of lymphatic metastasis.

APPROACH: The approach used is to study morphologically the way in which tumors implanted into the footpads of rodents metastasize to the draining popliteal nodes, and to obtain the actual metastasizing cells for study by cannulation of the lymphatic trunks. Using the Walker rat carcinoma as an initial model we have shown that tumor cells induce degeneration of the lymphatic endothelium, and have obtained the actual metastasizing cells and shown that transport of cells in the lymphatic trunk is a continuous phenomenon; a majority of the cells in the lymph are lymphoreticular cells. In this model we have quantitated metastasis in the draining node by differential counting of cell suspensions. We have now gone on to study the metastasis of the 13762 syngeneic mammary adenocarcinoma, using this model.

161. MECHANISMS OF GROWTH, METASTASIS AND REGRESSION OF HUMAN BREAST CANCER IN NUDE MICE

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The summary for this project is under entry no. 148.

F. OTHER CLINICAL LABORATORY TECHNIQUES FOR DIAGNOSIS AND PROGNOSIS

162. MICROANALYSIS OF CAMP ENZYMES IN HUMAN BREAST TUMORS

Rutherford, C. L., Taylor, R., Cripps, M., Gutmann, E., Woodford, T., Virginia Polytechnic Inst. & State University, School of Arts & Sciences, Dept. of Biology, *Blacksburg, Virginia*, 24061, United States of America

We plan to continue our fractionation of tumor homogenates on DEAE-Sephacel in order to separate isozymes of both alkaline phosphatase and cyclic nucleotide phosphodiesterase. For alkaline phosphatase we will determine the inhibition profiles of the separated activity peaks. In addition we will begin polyacrylamide gel electrophoretic analysis of these activity peaks using untreated fractions and fractions treated with various glycosidases, e.g., neuraminidase. Further, we will use donated antiserum to determine whether any cross-reactivity exists between the isolated activity containing peaks and the isozymes of liver, placental, and intestinal origins.

Variations of the radiometric assay for phosphodiesterase suitable to the assay of microgram quantities of tissue have been evaluated. The most sensitive of these methods involved the assay of 5 microliters of sample volumes containing 1-100 micrograms of tissue extract. Tumor enzyme was found to be stable frozen at minus 76 degrees C or refrigerated overnight at a pH range of 4.8 to 9.0. Results of assays on lyophilized pieces, homogenates, and the supernatants and pellets of 27,000 x g centrifugations indicate that more than 60% of the tumor enzyme is soluble. Kinetic studies demonstrate that at least two forms of the enzyme are present in both malignant and benign samples, each with KMs in the 5 micromolar and 50 micromolar cAMP range. Preliminary fractionation data reveal two to four peaks of activity on DEAE-Sephacel, again with no significant difference appearing between the two tumor types.

BIBLIOGRAPHIC REFERENCES: Larner, E.H. and Rutherford, C.L. 1978. An artifact produced by boiling adenyl cyclase reaction mixture prior to cyclic AMP-radioimmunoassay. Anal. Biochem. 91:684-690.

163. ADVANCED BREAST CANCER - A STUDY OF SERIAL PLASMA GLYCOSLYTRANSFERASE LEVELS IN PATIENTS BEING TREATED BY CHEMOTHERAPY

Rubens, R. D., Bulbrook, R. D., Kessel, D., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

Levels of plasma glycosyltransferases appear to be elevated in neoplastic disease, although the relationship between enzyme levels and extent of disease has not yet been established. The level of plasma sialyl tranferase has been found elevated in patients with advanced breast cancer and in animals bearing metastasising mammary tumors. This study is directed at assessing value of measuring plasma glycosyltransferases as an index of the extent of tumor load in patients with metastatic breast cancer receiving chemotherapy. These enzymes are being esti-

mated before starting chemotherapy and on the first day of subsequent courses of chemotherapy in patients from the previous project to see if a positive correlation with clinical response can be found.

164. ISOZYMES SPECIFIC TO HUMAN BREAST NEOPLASIA

Yang, N., Michigan Cancer Foundation, Dept. of Biology, *110 E. Warren St., Detroit, Michigan*, 48201, United States of America

The transformation of normal human mammary epithelium to carcinoma is currently understood primarily in morphological, growth and cell behavioral terms. Limited information is available on the biochemistry of this differentiation process. Specific gene activation and repression, reflected in expression of enzymes, their isozymes and structural proteins are the fundamental mechanisms by which the development and progression of a carcinoma are controlled. In this study, I intend to establish systematically the enzyme and isozyme differences between normal and malignant human mammary epithelium; the effect of mammotropic hormones on differential isozyme expression; and whether this is useful in diagnosis and prognosis of breast cancer.

The studies are being carried out using a defined system to culture normal and malignant mammary epithelium. Work in progress indicates that normal and malignant human mammary epithelia exhibit apparent differences in some specific enzyme and isozyme expression and such differences are applicable to normal and neoplastic breast tissues derived in vivo. Efforts are being made to identify and characterize additional isozymes unique in type or amount in neoplastic human breast cells. The possibility of using these isozymes as diagnostic and prognostic markers for breast cancer will be assessed.

165. BIOLOGIC MARKERS IN BREAST CANCER PATIENTS

Sussman, H. H., Stanford University, School of Medicine, Dept. of Pathology, *Stanford, California*, 94305, United States of America

OBJECTIVES: Conduct a longitudinal study of biologic markers in breast cancer patients. Evaluate tissue and serum markers currently proposed as being potentially useful and develop a new set of markers from placental membrane proteins and glycoproteins and investigate their presence in serum and tissue. These studies will be coordinated with a well defined clinical study of breast cancer sponsored by the Northern California Cancer Program and conducted by the Northern California Oncology Group. This will provide a set of patients whose clinical care will be rigorously controlled and will also ensure direct control of specimens and accurate patient information. There will be twelve major institutions participating in these studies. The NCOG protocols will evaluate the patients by routine tests, and these will be complemented by our evaluation of the markers that will be measured in this protocol.

166. DETECTION OF HUMAN MILK PROTEIN RNA TRANSCRIPTS IN MAMMARY TUMOR BIOPSIES

Craig, R. K., Davis, M. S., Courtauld Inst. of Biochemistry, *London, England, United Kingdom*

OBJECTIVE: Development of a nucleic acid hybridization assay for the routine clinical detection of human milk protein RNA transcripts in mammary tumor biopsies.

APPROACH: Isolate and clone, using standard DNA recombinant techniques, mRNA sequences coding for human milk protein. These will then be used to identify the presence or absence of RNA molecules containing milk protein sequences in mammary tumor biopsies.

167. EFFECT OF BREAST CARCINOMAS ON PLASMA NMR RELAXATION RATES

McLachlan, L. A., Gray, A. J., Simpson, J. S., Inst. of Nuclear Sciences, *Private Bag, Lower Hutt, New Zealand*

OBJECTIVES: A preliminary study now in the process of publication showed that as cancer progressed the plasma nuclear magnetic resonance (NMR) hydrogen spin-lattice and spin-spin relaxation times tended to decrease and that this decrease sometimes preceded a tumor recurrence by several months. Furthermore, this reduction in relaxation rates is the opposite to what happens for almost all other illnesses which tend to increase the relaxation rates.

The purpose of this project is to extend these earlier experiments with the aim of determining whether or not NMR has possible clinical use as a means of monitoring the progress of cancer.

APPROACH: A longitudinal study of about two years duration is being undertaken using one group of about 50 patients from the Ludwig breast cancer trial or on advanced breast cancer trial along with a control group of about a dozen healthy people. At regular intervals both hydrogen and sodium spin-lattice and spin-spin relaxation times of the plasma will be measured and compared with the results of other blood tests and the patients' clinical condition.

168. DATA ANALYSIS FOR BREAST CANCER DETECTION PROJECT

Foradori, G. T., University City Science Center, *3624 Market St., Philadelphia, Pennsylvania*, 19104, United States of America

OBJECTIVES: Collect, process, manage, and analyze data for the Follow-up Program of the Breast Cancer Detection Demonstration Project. Specifically, develop a follow-up data system, develop and maintain a monitoring system, develop edit procedures, keep the system current, develop procedures to correct errors, provide monthly, quarterly, and annual reports for projects and for NCI, carry out data analyses in consultation and under the direction of the Project Officer, and provide liaison functions with the Follow-up Centers.

169. INVESTIGATION INTO SIGNIFICANCE OF TRACE ELEMENT CONCENTRATIONS AND THEIR CHANGES IN DIAGNOSIS AND FOLLOW-UP OF MALIGNANCIES BY PIXE

Nanto, V. O., Dahlbacka, J., Turun Yliopisto, Dept. of Clinical Chemistry, *Kiinamyllynk 8-10, SF20500 Turku 52, Finland*

There is much information on the changes of trace elements, notably trace metals such as Zn, Cu, Cr, Mn, etc., in human biological fluids and tissue specimens in malignant diseases. However, the reports are often contradictory and inconsistent, and in most cases clinical advantages of trace element determinations in malignancies have not been identified. The objective of this study is to investigate trace metal concentrations and their changes during treatment of malignant diseases using a multi-element method, particle-induced X-ray emission analysis (PIXE), with which it is possible to obtain simultaneously several (6-10) trace metals from a biological specimen (both fluids and tissues) with minimal manipulation of the samples and with sensitivity of 0.1-0.01 ppm. By computer analysis not only changes in concentrations of isolated trace metals but also in their ratios can be investigated and their significance stated.

Trace element analysis will be made using PIXE analysis in the Cyclotron Laboratory of Abo Akademi (J. Dahlbacka). Atomic absorption spectrophotometry and neutron activation analysis will be used as complementary methods. The patient material will be analyzed by Prof. E. Nordman (Department of Oncology, University Hospital) and by Dr. A. Rajamaki (hematological cases).

Patients with breast cancer, gastrointestinal cancers, leukemias and Hodgkin's disease will be included in the material. Specimens of tissue are obtained from these patients which are operated on. From patients with hematological malignancies white blood cells are isolated for analysis. Serum samples are obtained from all patients and in selected cases the daily urinary excretion of trace metals is measured. Trace metals determined include Zn, Cu, Mn, Cr, Ni, Sr, Br, Mg, Ca.

170. PROGRAM OF PREVENTIVE TOCOGYNECOLOGY AS PART OF A GENERAL MEDICAL SERVICE

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OBJECTIVE: Based upon the results of the preventive tocogynecology program, it was determined that a gynecological checkup should be included as a part of the medical care of the general adult out-patient service. The purpose is to detect asymptomatic gynecologic pathologies, treat them, and educate the women regarding the importance of preventive gynecology.

METHOD: A multidisciplinary team will instruct all women who come to the service and will perform the exam, including tocogynecology, speculum, cytology and breast exam.

PROGRESS: During the first six months 2,346 patients were examined, 45% of whom presented with some form of gynecologic pathology. Another 35.5% were referred to the out-patient breast service, where 61 were found to have benign pathology and 6 presented with breast cancer. Benign gynecologic pathology was evident in 148 patients (dystopia and uterine myoma); of 13 altered cytologic examinations, 4 corresponded to cancer of the uterine cervix. This program is proving to be of great usefulness, low cost, and is feasible without sophisticated equipment. It is considered a valuable addition to all services attending a female population.(Translated)

171. B/C EVALUATION OF BREAST CANCER DETECTION STRATEGIES

Gohagan, J. K., Rodes, N. E., Spitznagel, E. L., Darby, W. P., Butcher, H., Washington University, School of Engineering & Applied Science, Dept. of Technology & Human Affairs, *4559 Scott Ave., St. Louis, Missouri*, 63130, United States of America

We will develop analytically based guidelines and practical procedures for personalized, quality controlled screening and diagnosis in clinical settings. Our goal is improved quality and cost effectiveness of breast cancer detection practices. We will investigate the relative benefits and costs of competing strategies, including the confirmatory value of a screen and economic measures of efficiency. We will categorize strategies according to their preferability for women within specific risk profiles according to all benefit-cost criteria development. We will develop risk profiles for the ten thousand women in our detection project, determine the value of modality specific features as predictors of the disease, determine which interpretive decision rules most enhance the technical quality of detection modalities and determine which strategies (logical combination of detection modalities in conjunction with decision rules for recommending a course of action) are best for which risk groups. To transfer our quality control and strategy selection methodologies to other clinical settings, we will prepare a detailed implementation manual.

172. BREAST CANCER PROGNOSTIC STUDY

Brennan, M. J., Wilson, G. S., Furmanski, P., Rosenbaum, M., Isenberg, R., LaRose, E., Kirkland, W., Russo, J., Weigand, R. A., Mortensen, R. F., Rudczynski, A. B., Brooks, S. C., Michigan Cancer Foundation, Research Division, *110 E. Warren St., Detroit, Michigan*, 48201, United States of America

The high frequency of early deaths associated with breast cancer results from the recurrence of metastatic disease. The Breast Cancer Prognostic Study was organized to identify those characteristics of breast cancer patients and their tumors which are associated with early recurrence. Such markers would aid in targeting follow-up and therapeutic modalities to those at greatest risk; and systematic study of a large number of individual breast cancers and their hosts, with complete clinical follow-up, would provide an unprecedented view of the basic biology of breast cancer.

Based on the active participation of the local clinical community, medical, surgical, and pathology associate groups, together with the Biological Resources Unit, are responsible for the recruitment of patients, clinical history, diagnostic evaluation, follow-up, recurrence data, and procurement of tumor, lymph node and blood specimens. A key element is the Pathology Panel which provides detailed pathological characterization of specimens.

The clinical specimens are distributed to research laboratories where the materials are characterized via morphology, immunology, biochemistry, endocrinology, and cell biology. The assays are chosen on the basis of past and current data associating them with malignant potential, tumor burden or resistance to tumor development. As of Feb. 1, 1979, 461 patients had been entered into the Study, averaging 3-5 new entries per week.

BIBLIOGRAPHIC REFERENCES: Russo, J., Fine, M., Husain, M., Krickstein, H., Robbins, T., Rosenberg, B., Park, Y., Brennan, M., and Rich, M. Analysis of recurrence of infiltrating ductal carcinomas containing tubular and cribriform patterns. Proc. American Assoc. Cancer Research 1979, in press. Weigand, R.A., Isenberg, W.M., and Brennan, M.J. Elastosis as a prognostic indicator in human breast cancers. Proc. American Assoc. Cancer Research, 1979, in press.

173. A NEW DIAGNOSTIC PROCEDURE FOR BREAST CANCER

Gaffney, E. V., Pennsylvania State University, University Park Campus, School of Science, Dept. of Microbiology & Cell Biology, *211 Whitmore Lab., University Park, Pennsylvania*, 16802, United States of America

The current proposal concerns the development of a diagnostic approach to breast cancer which will correlate the level of a growth inhibitory factor in sera with the presence or absence of breast carcinoma. Initial studies show that human serum (HuS) from normal donors specifically inhibits the growth of malignant mammary cell populations. This same activity is absent or diminished in sera from breast cancer patients. The activity is attributable to a protein component which is partially purified. This study takes advantage of the sensitivity of the MCF-7 cell line to examine sera samples from different population groups and thus determine what effect variations of sex, age and health status have on the level of activity. In addition, isolation and characterization of this factor will be pursued with a view to the eventual development of a diagnostic radioimmunoassay. The tissue specificity of this activity will be studied by determining the growth response to HuS of malignant cells derived from other cancer types.

174. RELATION OF INTESTINAL FLORA TO BREAST CANCER IN HUMANS

Gorbach, S. L., New England Medical Center Hospital, *171 Harrison Ave., Boston, Massachusetts*, 02111, United States of America

Determine the role of the intestinal microflora in the metabolism of biologically significant estrogens in women who are at high and low risk of developing breast cancer. We will collect urine, plasma, and feces from five different groups of women and will measure the levels of various biologically significant estrogens. In addition, fecal specimens will be collected in order to extract enzymes from the intestinal microflora to test their ability to modify estrogens by deconjugation, dehydroxylation, hydroxylation,. aromatization, and reduction of keto groups.

175. CLINICAL TRIAL OF WEIGHT REDUCTION AS AN ADJUVANT IN THE PRIMARY TREATMENT OF BREAST CANCER IN POSTMENOPAUSAL OBESE WOMEN

deWaard, F., Rijskuniversiteit te Utrecht, Inst. of Social Medicine, Dept. of Epidemiology, *Bijhouwerstraat, NL-2501, Utrecht, Netherlands*

OBJECTIVE: Test the hypothesis that prognosis is favorably influenced by weight reduction.

APPROACH: Randomized clinical trial. In the randomization process 60% of women are allocated to the weight reduction group.

PROGRESS: The project is in its initial stage.

176. EPR STUDIES ON DETECTION AND TREATMENT OF CANCER

Zimbrick, J. D., Stephens, R., Baker, L., Dean, D., Jewell, W., Mathew, A., University of Kansas, Lawrence Campus, School of Liberal Arts & Sciences, Dept. of Radiation Biophysics, *112 Bailey Hall, Lawrence, Kansas*, 66045, United States of America

Electron paramagnetic resonance (EPR) spectroscopy is being evaluated for use as a potential screening technique for early detection of cancer. EPR spin labeling techniques are being utilized to elucidate possible membrane and intracellular viscosity changes which may occur in blood components of humans with cancer. A double-blind study will be continued on the EPR signal intensity of Cu(II) bound to ceruloplasmin (Cu(II)-Cp) and on the ratio Cu(II)/total Cu in serum samples from female volunteers who are asymptomatic but have a higher than average risk of developing breast cancer. Animal tumor model systems already developed will be utilized to provide lymphocytes for spin labeling studies to determine possible changes in membrane fluidity or cytoplasmic viscosity associated with cancer. These tumor models will also be studied to determine how soon after tumor cell implantation the changes

in Cu(II)-Cp level and in the ratio Cu(II)/total Cu occur, and to obtain more information on possible hypotheses for these changes. Studies on the molecular properties of CP, including single crystals of CP, will be continued. These will include electron spin echo studies which may help to characterize the binding sites of Cu in the molecule.

BIBLIOGRAPHIC REFERENCES: Horn, R. A., E. J. Friesen, R. L. Stephens, W. R. Hendrick, and J. D. Zimbrick, Electron Spin Resonance Studies on Properties of Ceruloplasmin and transferrin in Blood from Normal Human Subjects and Cancer Patients, Cancer 43 (6), 2392-2398 (1979).

177. EPIDEMIOLOGY AND NATURAL HISTORY OF BREAST CANCER

Petrakis, N. L., University of California, San Francisco Campus, School of Medicine, Dept. of Epidemiology & International Health, *551 Parnassus Ave., San Francisco, California*, 94122, United States of America

The intent of this program-project grant is to investigate the epidemiology of breast cancer and benign breast disease. The work will include: the determination of epidemiologic characteristics of women diagnosed as having different histologically defined breast conditions; epidemiological and laboratory studies of the secretion of mutagenic substances into breast fluids, including their chemical characterization and potential DNA-damaging and repair activity on cells in human breast fluids and their metabolic activation by ray mammary tissue; epidemiologic investigations of estrogen-binding beta-globulin in blood and breast fluids; and research on the value and effects of breast cancer risk counseling.

178. EARLY BREAST CANCER - THE USE OF FINGERPRINTS TO DETECT WOMEN WITH BREAST CANCER

Hayward, J. L., Chaudary, M., Bierman, H., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

It has been suggested that some women with breast cancer have certain unusual features in their fingerprints (accidentals). If this were so, the presence of these features might be a useful way of identifying women in the general population who are at risk of developing breast cancer in the future.

In a pilot study, fingerprints were taken from 25 women with breast cancer, who were admitted to the Breast Cancer Unit at Guy's Hospital, and 25 normal women. These fingerprints were numbered at random and were reviewed 'blind' at the Institute for Cancer and Blood Research, Los Angeles, California. The analysis showed that twice the number of women with breast cancer had accidentals in their fingerprints compared with the controls. The numbers were small, however, and the difference was not significant. 200 further fingerprints were collected and sent to the Institute for Cancer and Blood Research where a second analysis was undertaken.

This showed no difference in the incidence of abnormalities between controls and breast cancer patients. However, the controls used for this second series were patients with benign breast disease who are known to have a higher subsequent incidence of breast cancer than the normal population. A further 200 cases are being collected in which the controls will be taken from the normal population being studied in Guernsey.

179. PREDICTION OF RECURRENCE RATES AFTER MASTECTOMY

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The summary for this project is under entry no. 122.

180. DATA ANALYSES FOR BREAST CANCER TREATMENT PROGRAM

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The summary for this project is under entry no. 68.

181. IDENTIFICATION OF TUMOR RELATED GLYCOPROTEIN TUMOR MARKERS IN MALIGNANT MELANOMA

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OBJECTIVE: To identify tumor related glycoproteins in serum and evaluate their use as clinical tumor markers.

APPROACH: Tumor related glycorproteins have been identified in malignant and transformed cells, in spent tissue culture medium used to grow neoplastic cells, and in the serum of cancer patients. These can be most readily monitored by measurement of glycoprotein bound sialic acid. Initial studies have demonstrated close correlation with tumor burden in malignant melanoma, breast carcinoma, and ovarian carcinoma. Investigation is in progress to evaluate the clinical value of these measurements in other malignancies. Further preliminary studies have suggested that the non-specific acute phase reactant glycoproteins can be quite readily separated from the more specific glycoproteins of tumor origin.

182. PURIFICATION OF HUMAN BREAST TUMOR PROTEINS

Lerner, M. P., Nordquist, R. E., University of Oklahoma, Health Science Center, School of Medicine, Dept. of Microbiology & Immunology, *Box 26901, Oklahoma City, Oklahoma*, 73190, United States of America

Breast cancer is a major cause of death of American women. However, there is little information on biochemical and immunological events that occur in human breast tissue during the neoplastic process. Our past studies have shown that sera from women with breast cancer have antibodies reactive with a human breast tumor cell line, BOT-2 cells. Our recent studies show that the proteins isolated from BOT-2 cells are reactive with sera from breast cancer patients. Preliminary studies indicate that the proteins isolated from BOT-2 cells are quite similar, biochemically, to proteins isolated by others from whole human breast tumor tissue. The objectives of this proposal are to isolate and purify the proteins from BOT-2 cells using standard chromatographic and electrophoretic methods. The data will indicate the biochemical nature of human breast tumor proteins and may be quite useful in future serodiagnostic, therapeutic, and immunologic studies of human breast cancer.

BIBLIOGRAPHIC REFERENCES: Lerner, M.P., J.H. Anglin, and R.E. Nordquist. 1978. Cell surface antigens from human breast tumor cells. J. Natl. Cancer Inst. 60: 39-44. Nordquist, R.E., J.H. Anglin, and M.P. Lerner. 1978. Antigen shedding by human breast cancer cells in vitro and in vivo. Brit. J. Cancer 37: 776-779.

183. PROTEIN SAA IN NEOPLASTIC DISEASE

Benson, M. D., Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Medicine, *1219 W. Michigan St., Indianapolis, Indiana*, 46202, United States of America

The objectives of this proposal are to determine the serum levels of protein SAA in neoplastic diseases, relate these data to diagnosis and prognosis and define the relationship of this protein to the immune dysfunctions noted in cancer. This protein (SAA) which is the precursor of secondary amyloid is present in all normal sera and has been shown to be increased in a number of acute and chronic diseases as well as in cancer. SAA in the murine model of secondary amyloidosis has previously been shown to suppress the formation of antibody in in vitro cultures of splenic lymphocytes.

SAA levels will be determined by radioimmunoassay using radiolabeled amyloid protein AA and antiserum specific for AA. Sera will be collected from patients with cancer of lung, bowel, breast and lymphoma at the time of initial diagnosis and at periodic intervals thereafter. SAA levels will be correlated with type of tumor, response to therapy, and presence or absence of recurrent tumor.

A relationship between SAA levels and lymphocyte dysfunction as measured by mitogen stimulation and T and B cell enumeration will be sought. The effect of SAA on the in vitro formation of antibody by human lymphocytes will be evaluated using a modification of the Marbrook culture technique with SRBC as antigen and response will be measured by the hemoly-

tic plaque assay. Purified human SAA will be used for these experiments to avoid other suppressors of the immune system which may be present in cancer serum. The objective of these experiments is to show whether SAA can cause suppression of the immune response in the human as well as in the murine system.

BIBLIOGRAPHIC REFERENCES: Benson, M.D., and Cohen, A.S.: Serum amyloid A protein (SAA) in amyloidosis, rheumatic and neoplastic diseases. Arthritis Rheum. 22:36-42, 1979. Benson, M.D.: Synovial fluid SAA levels in arthritis. Clin. Res. 27:141A, 1979 (Abstract).

184. CHARACTERIZATION OF PLASMINOGEN ACTIVATION ACTIVITY IN HUMAN BREAST TUMOR CYTOSOLS

Sutherland, D. J., Sunnybrook Hospital Medical Centre, *2075 Bayview Ave., Toronto, Ontario,* M4M 3M5, Canada

OBJECTIVE: Plasminogen-activating activities have been demonstrated in human tumors. This study seeks to characterize these activities in human breast tumors.

APPROACH: Human breast tumors being analyzed for steroid receptor proteins will serve as the sources of material. Studies of both cytosol and particulate fractions will be made using recognized separation procedures to characterize the types and molecular characteristics of the plasminogen-activating activities present in these tumors.

PROGRESS: Plasminogen-activating activities have been demonstrated in breast tumors and have been shown to be weakly correlated with steroid receptor activity. Preliminary studies indicate that further characterization of these activities is possible and suggest that characterization of a tumor's plasminogen-activating activity may provide specific markers for tumor-related functions.

185. SERUM LIPOPROTEINS IN PATIENTS WITH BREAST CANCER

Aladjem, F., Lee, Y., University of Southern California, School of Medicine, Dept. of Microbiology, *2025 Zonal Ave., Los Angeles, California,* 90033, United States of America

Significant serum lipoprotein concentration differences have been reported to occur between patients with mammary carcinoma, normal individuals with a family history of cancer, and normal individuals without family history of cancer.

The objective of this work is to study the chemistry of the serum lipoproteins of individuals in these three groups. The first objective will be to ascertain whether the differences are quantitative only or whether chemically different aproproteins, and consequently lipoproteins, occur. If qualitative differences are found, then the next objective will be to determine the chemical basis of the differences.

186. SERUM FROM PATIENTS WITH BREAST LESIONS

Whitney, L. W., Wilmington Medical Center, *501 W. 14th St., Wilmington, Delaware,* 19899, United States of America

OBJECTIVES: Serve as a verification center for new breast cancer specific markers. The intent is to seek innovative approaches in need of large-scale field trials, rather than to add a few more cases to the already well-established studies. Develop specimen resources, i.e., blood from breast cancer patients and from controls, which include apparently normal women, women with benign disease of the breast, women with other types of cancer (gynecological), and women with other diseases.

187. PREDICTION OF EVOLUTION OF BREAST CANCER AND RESPONSE TO TREATMENT

Diaz Gles Solis, J. W., Lage Davila, A., Pascual, M. R., Rios, M. A., Instituto de Oncologia y Radiobiologia, Laboratorio de Bioquimica, *Calle 29 y E Vedado, Havana 4, Cuba*

The summary for this project is under entry no. 81.

188. SIGNIFICANCE OF CELLULAR RETINOIC ACID BINDING PROTEIN, ORNITHINE DECARBOXYLASE AND POLYAMINES AS POSSIBLE MARKERS IN PRENEOPLASIA

Huber, P., Kung, W., Eppenberger, U., Universitat Basel, School of Medicine, Dept. of Gynecology, *Hebelstrasse 1, CH4000 Basel 4051, Switzerland*

The summary for this project is under entry no. 157.

III. THERAPY OF HUMAN BREAST CANCER AND RELATED STUDIES IN MODEL SYSTEMS

A. RADIATION THERAPY OF BREAST CANCER IN MODEL SYSTEMS

189. OPTIMIZATION OF RADIATION THERAPY

Dethlefsen, L. A., Stewart, J. R., Roti Roti, J. L., Higashikubo, R., Riley, R. M., Utah Higher Education System, University of Utah, School of Medicine, Dept. of Radiology, *1400 E. 2nd S., Salt Lake City, Utah,* 84112, United States of America

Our immediate goals are a detailed analysis of the radiation response and combined-modality response (i.e. adriamycin and x-irradiation) of two established in vivo lines (Slow and S102F) of the C3H mouse mammary tumor as well as that of the lining epithelium of the duodenal crypts. These analyses will be especially concerned with evaluating the therapeutic responses as they relate to the various growth kinetic parameters in the belief that such an approach will suggest a simplified model for optimizing protocols for fractionated radiation therapy and fractionated combined-modality therapy. The methods of analysis included growth delay, TCD50/120, 3H-TdR autoradiography and flow cytometry. These analyses will be for tumors x-irradiated under ambient (mice breathing air), hyperbaric oxygen and/or mixtures of oxygen and carbon dioxide, and hypoxic (tumor circulation clamped) conditions. The analysis for the duodenum includes LD50/6, crypt survival 3H-TdR autoradiography and flow cytometry. These studies on both normal and malignant tissues are done for adriamycin alone, x-irradiation alone and combined treatments with various intervals of time between modalities.

BIBLIOGRAPHIC REFERENCES: Dethlefsen, L.A.: In Quest of the Quaint Quiescent Cells, In: Radiation Biology in Cancer Research. The 32nd Annual Symposium on Fundamental Cancer Res. February 27-March 2, 1979 (In press). Dethlefsen, L.A.: The Growth Dynamics of Murine Mammary Tumor Cells in situ. In: Systematics of Mammary Cell Transformation. Presented at a workshop; Detroit, Michigan October 28-31, 1979; Academic Press (In press).

190. INFLUENCE OF REPEATED LOW DOSE IRRADIATION WITH X-RAYS AND NEUTRONS ON MAMMARY GLAND CARCINOGENESIS IN THE RAT

Broerse, J. J., vanBekkum, D. W., Hollander, C. F., vanZwieten, M. J., Central Org. for Applied Scientific Research TNO, Radiobiological Inst. TNO, *Lange Kleiweg 151, Rijswijk, Netherlands*

Experiments on the influence of repeated low dose irradiation on mammary gland carcinogenesis are of great interest because of the following two reasons: 1. In order to understand the process of carcinogensis it is important to investigate the relative contributions from repair of sublethal damage, repopulation and tissue turnover during the course of a fractionated irradiation with, for instance, 10 fractions every month. 2. In order to estimate the risks of routine diagnositic procedures such as mammography it will be important to obtain data from model studies in animals which could serve as a baseline for the human situation. In view of the possible synergistic effect of combinations of radiation and treatment with hormones the combined effect of fractionated radiation and estrogen treatment will also be investigated. It is expected that the influence of some of these factors will diminish considerably if radiation with a higher LET is employed. Consequently, it is recommended that parallel experiments with high LET radiations, preferably with neutrons of 0.5 MeV energy, are included in such a study.

In 1978 a total number of 900 rats have been exposed to different schemes of such fractionated irradiations with X-rays, gamma-rays and 0.5 MeV neutrons. The total project will take at least three years. The present application describes the program for the third year.

191. CELL KINETICS FOR TIMING POSTSURGICAL CHEMOTHERAPY

Schiffer, L. M., Braunschweiger, P. G., Betancourt, S. E., Allegheny-Singer Research Corp., Cancer Biology Section, *320 E.*

North Ave., Pittsburgh, Pennsylvania, 15212, United States of America

The studies proposed are designed to investigate the relationship between changes in tumor cell kinetics following cytoreductive tumor surgery and the most efficacious time for initiation of adjuvant chemotherapy.

Sequential chemo- and radiotherapy designed on the basis of cell kinetic perturbation in advanced disease will form the basis for adjuvant chemo- and radiotherapy schedules. Potentially advantageous times for the initiation of adjuvant treatment will be predicted on the basis of changes in the cell kinetics after cytoreduction. Predictions of efficacious and nonefficacious times will be tested in prospective treatment studies.

We will use four animal breast cancer models which will permit comparison of spontaneous and transplantable murine tumors, fast and slowly proliferating murine tumors and responses in mouse and rat models with similar proliferative rates. We will utilize our proven battery of cell kinetic measurements for 3H-TdR LI, DNA synthesis time, PDP index (growth fraction estimate) and mitotic index, all of which can be derived using in vitro methodologies on tumor specimens at the time of surgery.

The study has direct significance for the timing of adjuvant chemotherapy and chemotherapy for advanced disease in humans. Since this timing will be within a few days of the surgical procedure, initiation of early adjuvant treatments would be a direct surgical responsibility.

This proposal is in reference to RFA NIH-NCI-DCT-7.

192. MICROWAVE-INDUCED HYPERTHERMIA FOR DEEP-SEATED TUMORS

Douple, E. B., Strohbehn, J. W., Walsh, J. E., Bartrum, R. J., Roberts, D. W., Saunders, R. L., Dartmouth College, School of Medicine, Dept. of Medicine, *P.O. Box 833, Hanover, New Hampshire,* 03755, United States of America

This project proposes to use an invasive microwave irradiation system to achieve local hyperthermia for the treatment of deep-seated cancers. Microwaves in the GHz range are characterized by short energy absorption lengths in living tissue. It is proposed that this characteristic will be exploited and the energy will be delivered directly to the tumor site through transmission lines and antenna structures which have been developed in our laboratory. Antenna probes with diameters less than 1 mm will be employed. Thus, implantation can be performed with minimal disturbance to the surrounding tissue, and many of the problems associated with the delivery of heat to deep-seated tumors will be circumvented.

The objectives of this study are: (1) To further develop an invasive system for heating deep-seated tumors and to adapt the system for percutaneous insertion and surgical implantation so as to produce appropriate hyperthermia in difficult to heat, deep-seated tumors in humans; (2) to predict theoretically, and to measure experimentally, the heat distributions produced by the improved system in tissue phantoms, tumors and normal tissues of animals and humans; (3) to evaluate the therapeutic efficacy of the proposed system by studying the effect of the induced hyperthermia, alone, and in combination with ionizing radiation and chemotherapy on animal tumors, and in pilot clinical studies; and (4) to examine the effect of local hyperthermia on blood flow and the uptake of chemotherapeutic drugs in tumors and in normal tissues.

These tumors will include transplantable mouse mammary adenocarcinoma (MTG-B), chemically induced tumors in the rat, and spontaneous brain tumors in dogs. The effects of the treatment on tumor cell viability will be assessed using the TD50 and tumor latency assays as well as histological evaluation. Tumor growth, TCD50 and host lifespan will also be studied as indicators of therapeutic effectiveness, and normal tissue response will be carefully observed in heated animals. Clinical tumors will include brain tumors and other tumors such as pancreas and prostate cancer.

193. CANCER HYPERTHERMIA THERMOMETRY BY ULTRASOUND

Johnson, S. A., Christensen, D. A., Anderson, R. E., Berggren, M. J., Utah Higher Education System, University of Utah, School of Engineering, Dept. of Bioengineering, *1400 E. 2nd S., Salt Lake City, Utah,* 84112, United States of America

The summary for this project is under entry no. 11.

B. RADIATION THERAPY AND CHEMO-RADIATION THERAPY FOR HUMAN BREAST CANCER

194. RADIATION THERAPY ONCOLOGY GROUP

Perez, C. A., Marks, J., Phillips, G., Purdy, J. A., Simpson, J., Washington University, School of Medicine, Dept. of Radiology, *660 S. Euclid Ave., St. Louis, Missouri,* 63110, United States of America

The Division of Radiation Oncology at Washington University proposes to: 1) Continue participation in clinical trials of the Radiation Therapy Oncology Group; 2) contribute to the scientific contents of group studies and to actively engage in protocol design and coordination; 3) assist in administrative and organizational matters of the group outlined by the Chairman of the Group and Committee Chairmen; 4) participate in the analysis of scientific data generated by the Radiation Therapy Oncology Group and to prepare manuscripts to be submitted for publication to reputable scientific journals; 5) promote clinical trials within the framework of cooperative groups at Washington University School of Medicine. The Division has consistently been one of the major contributors of patients to RTOG protocol studies. Approximately 50% of the patients accessioned to the studies have been in non-metastatic protocols. The projected number of patients to be entered in protocol studies during the year 1979 will be in the range of 90 to 100. The Division participates in the avant-garde protocols in radiation oncology that require specialized facilities and equipment such as the hyperthermia and hypoxic sensitizers.

195. CARCINOMA OF THE BREAST

Prosnitz, L., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

196. PHOTORADIATION

Treurniet Donker, A. D., Star, W., Reinhold, H., Treurniet, R. E., Haije, W., van der Lugt, L., VanDaalen, J., Rotterdamsch Radiotherapeutisch Instituut, *Grene Hilledijk 301, Box 5201, 3075 EA Rotterdam, Netherlands*

Photoradiation utilizing hematoporphyrin (Hpd) activated by visible light in the red region of the spectrum has been found by T. Dougherty, Roswell Park Memorial Hospital, to be an effective treatment for controlling local and regional chest wall recurrences of breast carcinoma.

We are using an argon-dye laser as a source of red light of 630 nm wavelength and have started treating patients according to Dougherty's schedule.

We intend to investigate further therapeutic possibilities of this treatment using animal models.

Due to a favorable therapeutic width, it seems to be a comparatively harmless treatment modality. Its limitations in penetration could be overcome by interstitial or intracavitary (endoscopic) techniques.

197. EARLY BREAST CANCER - THE USE OF OVARIAN IRRADIATION AND PREDNISONE AS ADJUNCTIVE THERAPY AFTER MASTECTOMY

Hayward, J. L., Bulbrook, R. D., Meakin, J. W., Allt, W. E., Beale, F. A., Brown, T. C., Bush, R. S., Clark, R. M., Fitzpatrick, P. J., Hawkins, N. W., Jenkin, R. D., Pringle, J. F., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

Over a period of eight years, all women with early breast cancer who were referred to the Princess Margaret Hospital in Toronto for post operative radiotherapy were entered into a trial on the use of prophylactic ovarian irradiation and prednisone. Those women aged 45 and over were randomly allocated to three groups: group 1, no treatment; group 2, ovarian irradiation, group 3, ovarian irradiation plus prednisone. Patients aged under 45 were allocated only to groups 1 and 2. Recurrence times and survival in these patients were determined by external review.

It has been shown that in those women aged 45 or over, but who are still premenopausal, the use of ovarian irradiation and prednisone confers a highly significant degree of benefit in terms of both recurrence and survival. The degree of benefit induced by ovarian irradiation alone was not as pronounced. No benefit was conferred by either treatment method in patients who were postmenopausal.

The review of these cases is being undertaken biennially and will next be done in 1981. A further analysis of the results will then be carried out.

198. ADJUVANT THERAPY OF EARLY BREAST CANCER

Henderson, I. C., Sidney Farber Cancer Center Inc., Division of Medical Oncology, *44 Binney St., Boston, Massachusetts*, 02115, United States of America

OBJECTIVES: 1) To evaluate the drug combination cyclophosphamide and adriamycin as an adjuvant. 2) To evaluate the importance of therapy duration. 3) To determine the long-term effects of alkylating agents. 4) To evaluate the importance of radiotherapy added to chemotherapy to improve local control.

APPROACH: Patients are divided into high risk (more than 4 positive axillary lymph nodes or histologic involvement of the apical nodes) or moderate risk (1-3 axillary lymph nodes or a lesion clinically greater than 5 cm. in size with no positive lymph nodes). High-risk patients are randomized to receive either 15 weeks or 30 weeks of cyclophosphamide and adrimycin given IV every 3 weeks. The cyclophosphamide dose is 500 mg/sq.m; the adriamycin dose is 60 mg/sq. m. Moderate-risk patients are randomized to receive either CMF or MF for eight months. The cyclophosphamide dose is 100 mg/sq.m p.o. daily x 14/28 days; methotrexate 60 mg/sq.m IV days 1 and 8; and 5-FU 600 mg/sq.m IV days 1 and 8 of each cycle.

PROGRESS: To date 12 of 62 patients at high risk have relapsed; there is no clear difference in disease-free survival of patients given 15 or 30 weeks. Only four of 70 moderate risk patients have relapsed and no preliminary conclusions are appropriate.

199. STUDIES OF PATIENTS WITH DISSEMINATED SOLID TUMORS

Bodey, G. P., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Developmental Therapeutics, *c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

Independently and not as an agent of the Government, the contractor shall exert its best efforts to conduct Phase II and Phase III studies in patients with solid disseminated tumors. The tumors to be included in these studies shall be limited to lung carcinoma, melanomas and sarcomas of soft tissue, breast carcinoma, and sarcoma of boney origin. A minimum of 400 patients shall be included in these studies with no fewer than 25 patients from any one other tumor type. All patients shall be treated intensively with chemotherapy either alone or in combination with other drugs, radiotherapy, immunotherapy, or surgery in protocols to be agreed upon by the Project Officer and Principal Investigator. Protocols will include Phase II testing of new investigational drugs, Phase II testing of standard antitumor drugs not previously tested against the particular tumor type, as well as Phase III trials to determine the definitive activity of the above regimens.

200. CONTROLLED CLINICAL TRIALS IN MAMMARY CARCINOMA IN A REGIONAL TUMOR REGISTRY (ABBREV)

Hafstrom, L., Killander, D., Moller, T., Wiklander, O., University Hospital of Lund, Oncological Center for Southern Sweden, *E. Blocket, S22185 Lund, Sweden*

According to a national program as proposed by the National Board of Health and Welfare in 1974, oncological care in Sweden should be organized around several oncological centers, one center for each region in Sweden. Among the duties of these oncological centers are: cancer registration for the particular region, and development of special care programs for different types of malignant diseases.

In January 1978, a special program for the care of patients with mammary carcinoma stage II was started in the region in Southern Sweden. This program includes a controlled clinical trial as regards adjuvant therapy after initial modified radical mastectomy. Premenopausal patients are randomized between radiotherapy alone, radiotherapy combined with chemotherapy, and chemotherapy alone. Postmenopausal patients are randomized between: radiotherapy alone, radiotherapy combined with antioestrogen, and antioestrogen therapy alone.

Special proformas have been designed for the collection of data on these patients. Since the trial is a multicentric one, involving all departments of surgery and oncology in the region, the task of data collection is thus spread out among quite a number of participating departments and physicians.

The aims of the present investigation are as follows: a. to evaluate the type of data collection as regards the validity of data, to identify the different types of errors, and to study how these errors can be eliminated; b. to design special programs for continuous survey of the trial, for the statistical analysis and for the presentation of results to the participating departments; c. to introduce additional programs for the care of patients with mammary carcinoma in stage I and in stages III - IV with appropriate proformas for additional data collection and statistical analysis.

201. CYTOREDUCTIVE CHEMOTHERAPY BEFORE SURGERY AND RADIOTHERAPY IN BREAST CANCER T2/T3, N1B N2, N0

Alberto, P., Megevand, R., Krauer, F., Paunier, J., Riotton, G., Kanpanci, Y., Garcia, J., Rosset, G., Hopital Cantonal, Dept. of Medicine, *64 Ave. de la Roseraie, 1211 Geneva 4, Switzerland*

To investigate in a preliminary approach: a) The feasibility of non-surgical diagnosis of breast cancer by cytology, mammography, thermography and clincial examination. b) The psychological reaction of patients and doctors to a primary chemotherapy with delayed surgery in operable breast cancer. c) The effect of a short duration chemotherapy on the tumor volume. d) The effects of a short duration chemotherapy on the histological appearance of the tumor.

Open non-randomized pilot study, pre- and postmenopausal patients. Chemotherapy: Chlorambucil 5 mg/m2 daily, days 1-14, p.o. plus methotrexate 15 mg/m2 days 1 and 8, i.v. plus fluorouracil 500 mg/m2 days 1 and 8, i.v. plus adriamycin 10 mg/m2 days 1 and 8, i.v.

Modified radical mastectomy schedule on day 29. Postsurgical radiotherapy on conventional portals. Six months adjuvant chemotherapy with same drugs and same schedule.

Activated, November 1978.

202. POSTOPERATIVE RADIOTHERAPY AND CHEMOTHERAPY UTILIZING L-PAM IN PATIENTS WITH BREAST CANCER

Kuno, K., Fukami, A., Kasumi, F., Hori, M., Cancer Inst. Hospital, Dept. of Surgery, *1-37-1 Kamiikebukuro, Toshima-ku, Tokyo 170, Tokyo, Japan*

OBJECTIVE: To evaluate the effects of adding prolonged chemotherapy in patients with breast cancer.

APPROACH: Patients with one or more positive axillary nodes who undergo conventional radical mastectomy or modified radical mastectomy enter this study. Patients are randomly assigned to radiotherapy plus L-PAM and radiotherapy plus placebo. (1) L-PAM 0.15 mg/kg/day P.O. 5 days every 6 weeks, or (2) placebo in equivalent dosage form. Chemotherapy will be initiated two to four weeks postoperatively and will be given concomitantly with radiotherapy. Chemotherapy is to be terminated at the end of two years (16 courses) or upon the appearance of recurrent disease, whichever should occur first.

PROGRESS: Patients entered into the study in October 1976. As of October 1978, a total of 140 patients have been entered on study. There has not been sufficient time to produce conclusive information about the treatment effects. Longer follow-up time in all patients will be needed to obtain significant results.

203. THERAPEUTIC TRIAL FOR RAPIDLY PROGRESSING BREAST CANCER IN TUNISIA

Mourali, N., Tabbane, F., Belhassen, S., El Meddeb, A., Salah Azaiz Inst., *Blvd. du 9 Avril, Bab Saadoun, Tunis, Tunisia*

In previous reports (N. Mourali, 1974, 1977; F. Tabbane, 1976) rapidly progressing breast cancer was described by the Salah Azaiz Institute research group. These forms of breast cancer are characterized by rapid increase of the tumor and/or inflammatory signs (redness and edema), and a poor prognosis

of less than 20% five-year survival rate in the treated forms of patients who have no metastasis.

OBJECTIVE: To determine if chemotherapy used as primary treatment in conjunction with radiotherapy or surgery improves the survival of patients classified as having rapidly progressing breast cancer without metastasis. To determine which form of local regional treatment (radiotherapy or surgery) associated with chemotherapy best improves the survival of these patients.

APPROACH: Three cycles of regimen CMF are given after biopsy to patients who enter the study, followed by randomization between radiotherapy and surgery. Fifteen more cycles of chemotherapy follow local regional treatment. Seventy-four patients have entered the study so far.

204. COMBINATION THERAPY IN ADVANCED FEMALE BREAST CANCER - NOLVADEX AND CHEMOTHERAPY - A CLINICAL TRIAL

Shanta, V., Krishnamurthi, S., Gopalan, N., Cancer Inst., Dept. of Radiation & Medical Oncology, *Madras 600020, Madras, India*

OBJECTIVE: The evaluation of a combination of Nolvadex and DMFu in two groups of female breast cancer patients: (a) Locally inoperable breast cancer, patients receiving radiation; (b) radical mastectomy cases with high risk parameters for remote metastases.

APPROACH: A concurrent randomized controlled clinical trial is being conducted with the study group receiving DMFu and Nolvadex in a prolonged protocol in addition to radiation or radical surgery and the controls receiving either radiation or radical surgery with DMFu only.

PROGRESS: The trial has just commenced.

205. POSTOPERATIVE PROTRACTED COMBINATION CHEMOTHERAPY VERSUS POSTOPERATIVE RADIOTHERAPY IN AXILLARY POSITIVE LYMPH NODES IN EARLY BREAST CANCER

Patel, D. D., Gujarat Cancer & Research Inst., Dept. of Surgery, *New Civil Hosp. Campus Asarwa, Ahmedabad 380016, Gujarat, India*

OBJECTIVE: To assess long-term results of these two postoperative modalities of treatment in early cancers of breast and to define their value in prevention of local or systematic recurrence and to assess survival and cure rate.

APPROACH: All patients with clinically early cancers of the breast are operated on by standard radical mastectomy. Careful axillary dissection is carried out. The palpable nodes are marked out for their anatomical position and each node is histologically examined for evidence of metastasis. All the patients with more than four positive nodes are accepted for treatment and are treated either by postoperative radiotherapy or postoperative combination chemotherapy with methotrexate, 5-fluorouracil, mitomycin and cyclophosphamide in a bolus in one day. Patients receiving postoperative radiotherapy receive 3000-3500 rad to the drainage areas while those receiving chemotherapy receive a monthly bolus for the next year.

PROGRESS: About twenty-five patients have entered the study in each group. Early reports indicate that protracted chemotherapy may prevent or retard onset of systemic metastases.

206. AUTOLOGOUS MARROW TRANSPLANTATION

Buckner, D., Thomas, E. D., Stewart, P., Bensinger, W., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

We propose to evaluate the effectiveness of high dose chemoradiotherapy in a variety of malignant diseases including acute leukemia, chronic granulocytic leukemia, oat cell carcinoma, malignant lymphoma, ovarian carcinoma, breast carcinoma and resistant pediatric solid tumors. Patients will have marrow cryopreserved prior to therapy and reinfused following intensive therapy with regimens developed in the syngeneic and allogeneic transplant programs. The effectiveness of this approach in terms of marrow repopulation and therapeutic effectiveness will be evaluated.

207. PRIMARY BREAST CANCER THERAPY GROUP

Poisson, R. C., Cote, J., St. Lucs Hospital, Surgical Oncological Service, *1058 St. Denis St., Montreal, Quebec*, H2X 3J4, Canada

As a participating institution in the Primary Breast Cancer Therapy Group (NSABP), we are contributing data from patients entered into the various group protocols.

We have made a major contribution (35 patients) to Protocol No. 6, which is a protocol to compare worth of segmental mastectomy, with and without breast radiation, with total mastectomy plus axillary dissection. All patients undergo axillary dissection and those with histologically positive axillary nodes receive adjuvant chemotherapy.

Thirteen (13) patients have also been entered in Protocol No. 7, which compares L-PAM with L-PAM plus 5-FU; six (6) patients have been entered in Protocol No. 8, which is a trial to compare the worth of three-drug chemotherapy (L-PAM, 5-FU, and methotrexate) with two-drug chemotherapy (L-PAM and 5-FU).

We are also entering patients in Protocol No. 9, a trial to determine whether the anti-estrogen tamoxifen when combined with chemotherapy improves the results obtained with chemotherapy alone. Eighteen (18) patients so far have been entered in this newer protocol. In the last 2 years, a total of 72 patients have been entered.

Up to now we have been financed on a subcontract basis.

The present application seeks funding (a) to permit continued patient accrual in ongoing protocols, (b) to continue follow-up of patients entered into protocols which have terminated, and (c) to collect appropriate biological material and information relevant to such protocols.

This group has the same capability to accomplish any new breast cancer protocol as it has done for the protocols already mentioned.

208. ADJUVANT RADIO-, CHEMO- AND IMMUNOTHERAPY OF OPERABLE BREAST CANCER

Grohn, P. T., Heinonen, E. O., Klefstrom, P. S., Tarkkanen, J. O., Helsinki University Central Hospital, Dept. of Radiotherapy, *Haartmaninkatu 4, Helsinki, Finland*

OBJECTIVE: The aim of this study is to evaluate the value of post-operative radiotherapy, chemotherapy, combined radio- and chemotherapy and all of the above with non-specific immunotherapy with levamisole.

APPROACH: Normally, operated on breast cancer patients with stages II of III receive postoperative regional radiotherapy. It is known that mostly in cases with state III and very often in cases with stage II breast cancer the spreading of the cancer has already taken place at the time of diagnosis for these patients the value of local radiotherapy is questionable, because radiotherapy affects local recurrences but not the life expectancy of the patients. The early results of adjuvant chemotherapy as obtained by Bonadonna and others are encouraging. In our study the patients are randomized to various treatment groups and levamisole is administered double-blindly.

PROGRESS: Stage II breast cancer patients are randomized to two treatment groups, both receiving postoperative radiotherapy with levamisole or placebo. The data are being evaluated . Stage III breast cancer patients are randomized to following treatment groups: postoperative radiotherapy or postoperative chemotherapy or both, together levamisole or placebo.

The patients are examined as to recurrent disease, immunological status, routine laboratory examinations.

The research with stage III breast cancer patients is in progress.

209. ADJUVANT THERAPY OF BREAST CARCINOMA - PHASE III - TWO YEAR LOW DOSE VERSUS ONE YEAR HIGH DOSE CHEMOTHERAPY WITH RADIATION THERAPY

Melville, R. P., Atkinson, L., Coates, A., Sarfaty, G. A., Donnellan, M., Freedman, A., Mameghan, H., Prince of Wales Hospital, Special Unit for Investigation & Treatment, *Avoca St., Randwick, N.S.W., Australia*

OBJECTIVE: To compare the toxicity and the effect on disease free interval and survival of two chemotherapy regimens as adjuvant treatment following mastectomy for women with breast carcinoma and four or more involved axillary lymph nodes.

APPROACH: Eligiblity requires pathologic confirmation of primary and axillary nodes, resection within 6 weeks of study

entry, age 65 or under and informed consent. All patients will receive postoperative radiation to supraclavicular and internal mammary nodes. Stratification factors include menopausal status and estrogen receptor status. Randomization to: ARM I LACT: cyclophosphamide 300 mg IV, methotrexate 25 mg IV, 5-fluorouracil 500 mg IV and vincristine 1 mg IV day 1 each 3 weeks for 2 years, commencing after radiation therapy. ARM II LMF-Pred; chlorambucil 4 mg/M2 po daily days 1-14; methotrexate 40 mg/M2 IV days 1 and 8; 5-flurouracil 600 mg/M2 days 1 and 8. Prednisone 10 mg at midnight days 1-14. Cycles each 28 days for 1 year. Note: 2 cycles will be administered prior to radiation therapy.

PROGRESS: New study; no patients yet entered.

C. MASTECTOMY FOR HUMAN BREAST CANCER

210. EARLY BREAST CANCER - TRIAL COMPARING RADICAL MASTECTOMY WITH WIDE EXCISION

Hayward, J. L., Millis, R., Winter, P. J., Tong, D. Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

Follow-up continues on the 625 cases admitted to this trial. A further analysis is now being carried out. Almost all the original 370 admitted between 1960 and 1970 have been followed up for ten years and the 255 clinical Stage 1 cases admitted between 1970 and 1973 have been followed up for five years.

211. THERAPY OF CARCINOMA OF BREAST

Hubay, C. A., Case Western Reserve University, School of Medicine, Dept. of Surgery, *2109 Adelbert Rd., Cleveland, Ohio,* 44106, United States of America

OBJECTIVE: Conduct a prospective study of the relative effectiveness of mastectomy alone, mastectomy plus chemotherapy and an anti-estrogen, and mastectomy plus chemotherapy, an anti-estrogen and BCG in the treatment of patients with breast cancer which involves ipsilateral axillary nodes.

212. THERAPY OF STAGE II AND STAGE III BREAST CARCINOMA

Scanlon, E. F., Evanston Hospital, *2650 Ridge Ave., Evanston, Illinois,* 60201, United States of America

GOAL: To determine the effects of adding adjuvant chemotherapy and BCG to mastectomy for patients with locally advanced breast cancer.

WORKSCOPE: After stratification for prognostic factors and menopausal status patients are assigned to one of three treatment schedules: (1) oral phenylalanine mustard (L-Pam); (2) 5-fluorouracil, cyclophosphamide and prednisone (CFP); and (3) CFP plus BCG inoculations. Two of these three treatment schedules are identical with the Mayo Clinic adjuvant study and the data will be cumulative. The treatment courses are given for one year or until there is evidence of recurrence, whichever occurs first. Survival and disease-free intervals will be computed for each treatment group.

213. CONTROLLED CLINICAL TRIALS FOR BREAST CANCER AND OTHER TUMORS

Veronesi, U., Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

SCOPE: Controlled clinical trials for breast and gastrointestinal cancer using the following protocols: Adjuvant Chemotherapy with 12 cycles of CMF in breast carcinoma with N ion axillary lymph nodes; Operable breast cancer with N ion axillary lymph nodes: results of 6 vs 12 cycles of adjuvant CMF; Adjuvant treatment in postmenopausal women with operable breast cancer and histologically positive axillary lymph nodes: CMFP - AV with or without dose intensification; Adjuvant treatment with CMF ion tamoxifen in elderly greater than 65 years) postmenopausal women with operable breast cancer and histologically positive axillary lymph nodes; Prospective surgical adjuvant trial in premenopausal breast cancer with positive axillary nodes; Combined study with chemotherapy-radiotherapy vs. Chemotherapy - surgery in T3b-T4 breast cancer; Protocol for the treatment of inflammatory breast carcinoma; Protocol for small cell bronchogenic carcinoma; Protocols for the treatment of gastrointestinal tumors.

214. NATIONAL SURGICAL ADJUVANT BREAST PROJECT

Fisher, B., University of Pittsburgh, School of Medicine, Dept. of Surgery, *3550 Terrace St., Pittsburgh, Pennsylvania,* 15261, United States of America

Cancer control program for clinical cooperative groups - National Surgical Adjuvant Breast Project (NSABP).

215. SYMBOLIC GROUP THERAPY WITH MASTECTOMIZED WOMEN

Fornari, F., Burrone, A., Castaldi, S., Donadoni, M. A., Frontori, L., Marsella, F., Moletta, M., Quintavalle, G., Rutelli, R., Tamburini, M., Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

OBJECTIVES: Set up a procedure to guide emotional release to be used by mastectomized women trained to work with groups of breast cancer patients and determine the effect that symbolic therapy has on the elaboration of the anguish felt by women with breast cancer. If the results of this study are positive, we foresee its application over a large area that would provide an auxiliary psychotherapeutic service to a large number of patients with minimal cost to institutions.

APPROACH: Two 'exemplary' stories will be chosen from conversations with twelve women who have been surgically treated for mammary carcinoma. A sketch will be written based on these stories which will then undergo (coinemic) analysis of the symbolic referents within the text. Both the two stories and their interpretation will be acted out by an actress and an actor and then videotaped. Two women, who underwent mastectomies some years before and have been carefully trained, will show the film and lead a discussion with two groups of 25 women each who have just been operated on for breast cancer. A questionnaire will then be given to the 50 women who take part in the experiment and to a control group of 30 women. The psychological state of the study group will be tested before and after the discussion and both groups will be retested at intervals of one and six months.

The analysis of the results will show the modification in the quality of life effected by the experiment.

216. A RANDOMIZED PROSPECTIVE STUDY OF THE EFFECT OF EARLY VERSUS DELAYED PHYSICAL THERAPY IN THE PATIENT UNDERGOING AXILLARY DISSECTION

Rosenberg, S. A., Lotze, M., Gerber, L. H., Duncan, M., Nowroozi, F., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Dept. of Rehabilitation, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Patients with melanoma or breast carcinoma undergoing axillary dissection are randomized to receive early or delayed shoulder mobilization following surgery. The study is designed to answer the questions: Does physical therapy immediately post-op interfere with wound healing? Does physical therapy immediately post-op offer more effective treatment for shoulder function in this population? Eighteen patients have been entered into the study, but data is not yet definitive.

217. EVALUATION OF COUNSELING FOR MASTECTOMY PATIENTS

Bond, G. R., Blum, L., Visotsky, H., Berlin, N., Oviedo, M., Crivolio, A., Cohen, J., Pomp, H. C., Northwestern University, Chicago Campus, School of Medicine, Dept. of Psychiatry, *303 E. Chicago Ave., Chicago, Illinois,* 60611, United States of America

This study employs a comparative experimental design to evaluate the effectiveness of four short-term counseling approaches in helping mastectomy patients cope with the psychosocial problems brought on by the diagnosis and treatment of cancer. Each approach addresses a major coping task facing the cancer patient. The 'individual psychodynamic' approach addresses the symbolic meanings triggered by the diagnosis of a life-threatening disease, the loss of a breast and other physical changes. The mode of intervention will be focused interpretations around a single important psychological theme which has emerged as a result of the cancer. The 'group' approach will address feelings of isolation and stigma known to accompany diagnosis of cancer, using the commonality of the diagnosis as a basis for affiliation and sharing common experiences, mutual

identification, comparison of life circumstances, and other processes which have been identified as powerful therapeutic mechanisms in self-help groups and professionally led psychotherapy groups. The 'lecture' approach will address the feelings of helplessness and loss of control over one's circumstances, by providing factual information about the physical condition and suggesting solutions to problems in day-to-day living. The relaxation condition will teach a technique for reducing general body tensions in order to cope with the stresses of cancer and its treatment.

218. ADJUVANT ENDOCRINE THERAPY WITH AN ANTIESTROGEN IN OPERABLE BREAST CANCER PATIENTS ON THE BASIS OF ESTROGEN RECEPTOR ASSAY

Nomura, Y., Yamagata, J., Kondo, H., Kanda, K., National Kyushu Cancer Center, Department of Breast Surgery, *Ohaza-Notame 595, Minami-Ku, Fukuoka 815, Fukuoka, Japan*

OBJECTIVE: To assess the value of an anti-estrogen Mepitiostane (Thioderone) as an adjuvant endocrine therapy in preventing recurrence of malignancy in patients with operable breast cancer.

APPROACH: Approximately 200 patients with stages I, II, and III breast cancer who had been subjected to the radical or extended radical mastectomy were given Mepitiostane. An intermittent 6-month schedule with a 3-month administration of the drug, 5mg/day, p.o. with a 3-month interruption was repeated for 3 years following mastectomy. Ninety-seven patients with same stages of breast cancer before then were administered Mitomycin C, 0.4-0.6 mg/kg, one shot i.v. and were considered as the control group.

PROGRESS: The postmenopausal patients in the Mepitiostane group showed a much lower recurrence rate than those of the Mitomycin C group. Follow-up studies and investigations on correlations between the presence of estrogen receptor in tumors and the recurrence rates in both groups are now in progress.

219. FOLLOW-UP TECHNIQUE FOR LEVAMISOLE IMMUNOTHERAPY OF POST-SURGICAL COLON AND BREAST CANCER, BY MEANS OF DNCB QUANTITATIVE TEST

de Carli, H. O., Restbergs, V., Hospital San Roque, Lab. Oncologia Experimental, *19 y 508 C.C. 350 Gonnet, 1900 La Plata, Argentina*

The main method for the immunotherapy follow-up is the quantitative DNCB test using, after sensitization, five paper disc with 200, 100, 50, 25 and 2.5 micrograms of DNCB. DNCB test and rosette E test were performed before and after levamisole administration. Including rest periods, treatment is continued until, if possible, the hyperergic state or positivity to 2.5 micrograms of DNCB is reached. A plotting of reaction grades vs. time is done.

In case lymph nodes are negative the hyperergic state is obtained within two months. When there are positive lymph nodes the hyperergic state is reached between the 12th and the 18th month. With metastasis the curve frequently shows a negative slope and the patient dies in spite of immunotherapy. Thus, the prognostic value of the shape of the curves has to be assessed, since a negative slope of the curves could signal a future metastasis.

The protection conferred by the hyperergic state to DNCB was proved in five (to eight) year survival rate causistics, using tumoral perchloric soluble glycoproteins and levamisole.

In minimum residual cancer, after the obtained normalization of immunological parameters, the posology of maintenance for indefinite time could be as follows: three 50 mg pills daily for three consecutive days and then a four day rest period; the regimen continued for three weeks; immunological control must be performed before and after every three weeks' treatment, i.e., yearly treatment consists of three weeks of drug administration and nine weeks of rest.

220. POST-SURGICAL COLON AND BREAST CANCER IMMUNOTHERAPY WITH ANTIGEN-RICH PERCHLORIC SOLUBLE TUMORAL EXTRACTS

de Carli, H. O., Restbergs, V., Hospital San Roque, Lab. Oncologia Experimental, *19 y 508 C.C. 350 Gonnet, 1900 La Plata, Argentina*

In 1971 a protocol of post-surgical colon and breast cancer immunotherapy using autologous tumoral perchloric soluble glycoproteins was initiated. Especially on colon, breast, ovary and lung cancer, perchloric soluble extracts are rich in antigens. It was discovered that these glycoproteins restored delayed immunity generally diminished in cancer patients.

Our quantitative DNCB test using paper disc with 200, 100, 50, 25 and 2.5 micrograms of DNCB allowed us to determine the normal values according to sex, decades and pregnancy and to follow up quantitatively the immunological normalizing process in cancer patients. It was discovered that not only these patients could be restored immunologically but also they could be brought to the hyperergic state (positivity to 2.5 micrograms of DNCB) within a period inversely proportional to the quantity of positive lymph nodes. This follow-up was plotted graphically, using time as the abscissa. The values of E rosettes also normalized and were plotted in the graph. Immunological control and treatment every four months are recommended.

Of a group of 65 patients (all stages of colon cancer) about 87% survived more than five years, giving P less than 0.001, giving the 47% survival rate at the five year period (National Inst. of Health) after conventional surgery and for all stages of colon cancer. In breast cancer patients we obtained analogous figures. Separating colon tumor glycoproteins in a Sephadex G-200 column, we obtained two peaks. Preliminary studies apparently indicated that the first peak, rich in CEA, increases the DNCB test results and that the second one augments the E rosettes. After incubation of lymphocytes with the second peak, E rosette augmentation was observed.

As the action and results observed are similar to those due to levamisole, we attribute to the hyperergic state resulting from the administration of DNCB some guarantee of obtaining an extended survival rate.

221. PRE- AND POSTOPERATIVE CHEMOTHERAPY FOR STAGE II BREAST CANCER

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OBJECTIVES: To test the hypothesis that preoperative chemotherapy may increase survival by preventing enhancement of existing micrometastases or the development of new ones, both of which are likely to occur in the perioperative period.

APPROACH: Stage II breast cancer patients after clinical staging and needle aspiration biopsy are randomly allocated to two groups: (a) receiving one course of preoperative polychemotherapy, mastectomy plus intraoperative chemotherapy and 11 cycles of postoperative polychemotherapy and (b) undergoing mastectomy and 12 cycles of the same polychemotherapy.

PROGRESS: 140 patients have been entered until June, 1980. No differences in wound healing or other postoperative problems have been noted between the two groups. Numbers are still small to evaluate recurrence rates.

222. SURGICAL ADJUVANT PROJECT FOR BREAST AND BOWEL CANCERS

Desser, R. K., Bitran, J. D., Chiang, T. C., Hambrick, E., Michel, A. G., Recant, W., Michael Reese Hospital & Medical Center, Dept. of Medicine, *2929 S. Ellis Ave., Chicago, Illinois*, 60616, United States of America

As a participating institution in the National Surgical Adjuvant Project for Breast and Bowel Cancers, we are contributing data from patients entered into various group protocols. During a previous period of grant support in 1972 to 1977 we made a major contribution to protocol No. 4. In July of 1976, group participation was broadened to include medical oncologists and since that time contributions have been made to adjuvant therapy protocols. Support for these efforts has been on the subcontract basis. The present application seeks funding to permit the continued accrual of patients into active group protocols both in breast and colo-rectal cancers as well as to permit a continued follow-up of patients previously entered into now completed protocols. This application also presents a detailed progress report of our activities during the period of sub-contract support in the past 30 months.

223. COMBINATION THERAPY IN ADVANCED FEMALE BREAST CANCER - NOLVADEX AND CHEMOTHERAPY - A CLINICAL TRIAL

Shanta, V., Krishnamurthi, S., Gopalan, N., Cancer Inst., Dept. of Radiation & Medical Oncology, *Madras 600020, Madras, India*

The summary for this project is under entry no. 204.

224. POSTOPERATIVE RADIOTHERAPY AND CHEMOTHERAPY UTILIZING L-PAM IN PATIENTS WITH BREAST CANCER

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The summary for this project is under entry no. 202.

225. CYTOREDUCTIVE CHEMOTHERAPY BEFORE SURGERY AND RADIOTHERAPY IN BREAST CANCER T2/T3, N1B N2, N0

Alberto, P., Megevand, R., Krauer, F., Paunier, J., Riotton, G., Kanpanci, Y., Garcia, J., Rosset, G., Hopital Cantonal, Dept. of Medicine, *64 Ave. de la Roseraie, 1211 Geneva 4, Switzerland*

The summary for this project is under entry no. 201.

226. CONTROLLED CLINICAL TRIALS IN MAMMARY CARCINOMA IN A REGIONAL TUMOR REGISTRY (ABBREV)

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The summary for this project is under entry no. 200.

227. PRIMARY BREAST CANCER THERAPY GROUP

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The summary for this project is under entry no. 207.

228. THE ROLE OF OESTROGEN RECEPTORS IN ADJUVANT ENDOCRINE THERAPY FOR EARLY CANCER OF THE BREAST

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The summary for this project is under entry no. 54.

229. SEQUENTIAL IMMUNOLOGIC PROFILE OF CANCER PATIENTS UNDERGOING SURGERY AND ADJUVANT CHEMOTHERAPY

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The summary for this project is under entry no. 134.

D. ENDOCRINE ABLATIVE THERAPY WITH OR WITHOUT CHEMOTHERAPY FOR HUMAN BREAST CANCER

230. MECHANISM OF CONTROL BY ENDOCRINE ABLATION IN HUMAN BREAST CANCER

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This is part of a broader project. A summary of this subproject is not available.

231. ENDOCRINE ABLATION AND CHEMOTHERAPEUTIC AGENTS IN THE TREATMENT OF BREAST CANCER

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This is part of a broader project. A summary of this subproject is not available.

232. MEDICAL ADRENALECTOMY FOR RECURRENT BREAST CARCINOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

233. IMPROVEMENT OF OPERATIVE RESULTS OF HYPOPHYSECTOMY FOR DISSEMINATED BREAST CANCER

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OBJECTIVES: 1) The objective responsiveness to complete hypophysectomy in patients with disseminated breast cancer should be further improved. 2) Diabetes insipidus and other major side effects in the postoperative course of the hypophysectomy should be reasonably prevented and managed.

APPROACH: The therapeutic procedure which ablates the pituitary gland is the complete hypophysectomy through transsphenoidal approach (Hardy). 2) Research is carried out to obtain any clinical and laboratory findings which would more correctly than in the past predict effects of hypophysectomy: They are 1-DOPA test and estrogen receptor assay of the tumor tissue. With the aid of recent advances in clinical neuroendocrinology ADH-secretional function in the postoperative stage will be determined.

PROGRESS: 1) Hypophysectomy was carried out in 9 patients with disseminated breast cancers. Complete response was obtained in 3 cases, partial response in 3 cases, mixed response in 1 case, progressive in 1 cases, and in the other 3 cases, clinical evaluation was not done because they had been recently operated on. 2) Postoperative diabetes insipidus was reasonably prevented and reduced with the administration of indomethacin.

E. MEDICAL SUPPRESSION OF ENDOCRINE FUNCTION IN HUMAN BREAST CANCER TREATMENT

234. SUPPRESSION OF ENDOCRINE FUNCTION IN HUMAN BREAST CANCER

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GOAL: To produce suppression of endocrine function with aminoglutethimide (AG), to establish the mechanism of steroid inhibition, and to compare the effects of surgical adrenalectomy, antiestrogen therapy, and aminoglutethimide in breast carcinoma.

WORKSCOPE: Female patients with inoperable, recurrent, or metastatic breast carcinoma and whose tumors are either estrogen receptor positive or unknown are selected for study. Women are randomized into two separate therapeutic trials: a comparison of medical adrenalectomy (AG plus hydrocortisone) vs. surgical adrenalectomy, and of AG vs. the antiestrogen, tamoxifen. Extensive endocrine studies evaluate the effects of AG on extra-adrenal estrogen production, androgen, progestin, and prolactin secretion, and steroid metabolism.

235. SWOG 7732, CMF WITH AND WITHOUT TAMOXIFEN IN PATIENTS WITH ESTROGEN RECEPTOR POSITIVE BREAST CANCER, PHASE III STUDY

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This study is for patients with histologically proven breast cancer who have measurable disease and who have not had any of the drugs in the current protocol. This study is designed to determine if the anti-estrogen tamoxifen, in combination with cytoxan, methotrexate, and 5-fluorouracil, will alter the response rate, duration of response, and median survival seen in patients treated with cytoxan, methotrexate, and 5-fluorouracil alone in advanced human breast cancer. Patients who are estrogen receptor positive are eligible for this study. The primary objective of the study is to compare response rates on the two treatment arms. Assuming that the response rate in ER positive patients on CMF alone is 50 percent and that it is desired to detect a difference of plus or minus 20 percent in the response rate of the CMF plus Tamoxifen treatment arm, then assuming a power equal to 80 percent and a significance level equal to 5 percent at least 93 response evaluable patients will be required in the two treatment arms in order to perform the necessary two-sided test.

236. STUDIES WITH COMPOUND 83636

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We have been evaluating the efficacy of lergotrile mesylate (Compound 83636, Lilly Corp.), a potent inhibitor of prolactin which works at the level of the pituitary gland, in the treatment of galactorrhea. Seven patients at this center have been treated and in each this drug was found to lower prolactin. Initial mean prolactin was 57 ng/ml before therapy and while on the drug the mean fell to 9.8 ng/ml representing an 83% fall in prolactin. Four of the patients with pituitary tumors fell to a mean of 22% of the initial value, and 3 with idiopathic galactorrhea and amenorrhea had a prolactin drop to 12% of the initial value. Galactorrhea disappeared in 4 and menses resumed in 4 of 5 patients where this was possible. Two patients became pregnant. This part of the project has been temporarily halted because of 2 year rat toxicity studies that revealed a small number of tumors of genital organs.

We have been continuing the use of this drug in patients with acromegaly and breast cancer. Lergotrile mesylate paradoxically lowers growth hormone in some patients with acromegaly. So far we have used this drug on 4 patients at this center. In 2, growth hormone fell to levels of less than 5 ng/ml (normal). In the third patient there was a greater than 50% drop on doses of 2 mg t.i.d.; the fourth patient did not respond to these dose levels. In the 3 in which growth hormone fell the patients reported decreases in some of their symptoms.

237. EARLY BREAST CANCER - THE EFFECT OF CHEMOTHERAPY ON ENDOCRINE FUNCTION

Rubens, R. D., Hayward, J. L., Bulbrook, R. D., Wang, D. Y., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

Because breast cancer is sometimes hormone-dependent, it has been postulated that adjuvant chemotherapy may act, in part, through suppression of endocrine function. Hormone studies are being performed in patients in the adjuvant chemotherapy trial (see preceding report). Blood for hormone estimations (estrogens, progestrogens, androgens, gonadotrophins and prolactin) is taken preoperatively and, subsequently, on the first day of the 3rd, 6th and 12th course of chemotherapy, and at the same times for the control patients. Preliminary results have suggested that there is suppression of ovarian function in premenopausal patients receiving L-phenylalanine mustard as adjuvant chemotherapy after radical mastectomy for Stage II breast cancer.

238. SUPPRESSION OF ENDOCRINE FUNCTION AS TREATMENT OF BREAST CANCER (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

239. PHASE I-II - TAMOXIFEN IN ADVANCED BREAST CANCER (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

240. ENDOCRINE FACTORS INFLUENCING TUMOR GROWTH IN MAN

Pearson, O. H., Manni, A., Brodkey, J., Arafah, B., Case Western Reserve University, School of Medicine, Dept. of Medicine, *2109 Adelbert Rd., Cleveland, Ohio*, 44106, United States of America

Antiestrogen therapy has yielded results equivalent to those of surgical hypophysectomy in the treatment of women with stage IV breast cancer. Antiestrogens have induced remissions in some 'completely' hypophysectomized patients in whom low levels of estrogen were detectable in the serum. However, hypophysectomy has induced remissions after initial treatment with antiestrogen, suggesting that pituitary hormones may play a role in the growth of some breast cancers. Pharmacological doses of androgen have also been effective after antiestrogen therapy, suggesting that other endocrine factors may play a role. Antigrowth hormone, antiprolactin and antiandrogen drugs will be tested for potential antitumor effects. Estrogen, progesterone, androgen and prolactin receptors are being measured in the tumors for their potential usefulness in predicting response to endocrine treatment. The DMBA-induced rat mammary cancer model system is being used for studies on the regulation of receptor levels. Studies on combinations of endocrine and cytotoxic chemotherapy are being carried out in patients with stage II and stage IV breast cancer for the possible enhancement of therapeutic results.

241. ESTROGEN BIOSYNTHESIS

Orr, J. C., McGirr, L. G., Memorial University of Newfoundland, School of Medicine, Basic Sciences Division, *Health Science Complex, St. John's, Newfoundland*, A1C 5S7, Canada

OBJECTIVE: To gain a better understanding of the exact chemical pathways by which androgens are converted to estrogens in humans. The one step about which controversy still remains is the 'third oxygenation' reaction, the conversion of 17 beta,19,19-trihydroxyandrost-4-en-3-one ('19,19-dihydroxytestosterone') to formic acid and estradiol. We are using a probe capable of testing several of the proposed intermediates (see below). We may ultimately be able to design highly specific aromatase inhibitors, providing an alternative to the present anti-estrogens used in breast cancer therapy.

APPROACH: The proposed intermediates in the last step of estrogen biosynthesis involve attachment of oxygen at various alternative positions in ring A, followed closely by loss of that same oxygen in a dehydration-like step. The presence of a fluorine substituent at the epimeric position to that postulated to undergo oxygenation would prevent loss of the oxygen in the ultimate step of estrogen biosynthesis, and provide us with the evidence regarding the structure of the intermediate in that elusive step.

PROGRESS: The product of aromatization of 2 alpha-fluorotestosterone by placental microsomes has now been identified as 2-fluoroestrone. The time course of the aromatization (and 17-oxidation) has been followed. A 'shunt' pathway to the 2 alpha-fluoro-3-hydroxy-delta 4-androgens has been identified. We conclude that the mechanism of aromatization proposed by Fishman, involving 2 beta-hydroxylation as the 'third oxygenation' is unlikely to occur. The possibility that there is protein-mediated stabilization of (geminal) hydroxyl and fluoro substituents on C(2) of the steroid is considered unlikely, but is being examined. Presented at Toronto International Congress of Biochemistry, 1979.

242. INHIBITORS OF AROMATIZATION FOR THERAPY OF BREAST CANCER

Salhanick, H. A., Neumeyer, J. L., Henderson, I. C., Corkery, J. C., Harvard University, Boston Campus, School of Public Health, Dept. of Population Sciences, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

Patients with metastatic breast cancer who have not shown objective responses to tamoxifen would be additionally treated with aminoglutethimide. Responses would be ascertained by objective criteria. Plasma levels of estrogen, tamoxifen, dehydroisoandrosterone, corticosteroid binding globulin and carcinoembryonic antigen will be monitored. Selective criteria for responsive patients will be identified. In laboratory experiments, structure-activity relationships of other inhibitors of aromatase will be studied with the intention of identifying inhibitors with maximal therapeutic ratio. Several series of new inhibitors will be synthesized. The aromatase enzyme will be purified by detergent solubilization, partially characterized and the characteristics of the active site studied with the intention of developing novel inhibitors.

243. NEUROENDOCRINE CONTROL OF MAMMARY AND PITUITARY TUMORS

Meites, J., Leung, F., Sonntag, W., Fanjul, L. F., Forman, L., Ruiz de Galarreta, C. M., Michigan State University, School of Veterinary Medicine, Dept. of Physiology, *New Administration Bldg., East Lansing, Michigan*, 48823, United States of America

OVERALL OBJECTIVE: To determine the relation of the brain, particularly the hypothalamus, to development and growth of mammary and pituitary tumors, and to utilize this

information to inhibit development and growth of mammary and pituitary tumors. Since prolactin and estrogen are the principal hormones involved in development and growth of mammary tumors, and to a large extent of pituitary tumors, and since these hormones are controlled directly (PRL) or indirectly (estrogen) by the hypothalamus, our aim is to experimentally alter hypothalamic function (by placing lesions or implanting hormones and drugs in the hypothalamus, by administration of drugs and hormones systemically and by use of appropriate environmental stimuli) to inhibit or accelerate development and growth of these tumors in mice, rats and dogs. The effects of high and low fat diets, reduced caloric intake and hypothalamic induced obesity on development and growth of mammary tumors, and on serum hormone levels, will be tested. The neuroendocrine mechanisms whereby pregnancy and lactation influence mammary tumor growth will be investigated. The effects of hypothalamic factors, hormones and drugs on hormone secretion and growth of pituitary tumors also will be studied. Old female rats also will be utilized since they develop spontaneous mammary and pituitary tumors, which we believe are related to functional changes in hypothalamic functions in old rats. We hope that some of the knowledge gained from these studies will prove useful in developing treatments for inhibiting the onset and/or growth of mammary and pituitary tumors in human subjects.

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244. MECHANISM OF ANTIESTROGEN ACTION IN BREAST CANCER

Chamness, G. C., University of Texas, Health Science Center at San Antonio, South Texas Medical School, Dept. of Medicine, *7703 Floyd Curl Dr., San Antonio, Texas*, 78284, United States of America

Although antiestrogens are known to be effective against many metastatic breast cancers and the antiestrogen tamoxifen has now been approved for general clinical use, little is known of their mechanism of action beyond the fact that they mimic estradiol in binding cytoplasmic estrogen receptor and translocating it to the cell nucleus. We therefore propose to compare selected antiestrogens with active estrogens at four critical steps of estrogen action: 1) temperature-dependent estrogen-induced receptor transformation; 2) receptor translocation and retention in cell nuclei, 3) receptor binding to specific nuclear acceptor sites; 4) nuclear processing, the depletion of receptor from the nucleus. Three model systems will be compared: the normal rat and mouse uterus, the DMBA-induced rat mammary tumor system, and the MCF-7 human breast cancer cell line. The goal will be discovery of the critical differences between estrogen and antiestrogen action, particularly in mammary tumor cells and as correlated with tumor responsiveness to antiestrogen therapy.

245. ISOLATION AND CHARACTERIZATION OF PROLACTIN INHIBITING FACTOR (PIF) AND PROLACTIN RELEASING FACTOR (PRF)

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The existence of a prolactin inhibiting factor (PIF) and a prolactin releasing factor (PRF) is suggested by many experimental approaches (pituitary transplantation, pituitary stalk section, lesions of the hypothalamus, electrical stimulation of specific hypothalamic areas and infusion of hypothalamic extracts). Therefore, isolation and knowledge of the structure of these hypothalamic hormones appear to be of prime interest. In fact, the objective remission of breast cancer induced by L-dopa or ergot derivatives suggests a possible use of PIF or PRF antagonists in the therapy of breast cancer. Porcine hypothalami extracted will be subsequently purified by techniques based upon the molecular size of the polypeptides, their partitioning properties and their amphoteric characteristics. An assay using dispersed anterior pituitary cells in monolayer culture will be used to screen the biological inhibiting or stimulating activity of prolactin secretion in each fraction. The fractions active in vitro will be then assayed in in vivo tests specially designed for the hypothalamic hormone. TLC and TLE will be mainly used to determine the purity of the fractions.

After purification, isolation and elucidation of the structures of PIF and PRF, synthesis of the new molecules, and comparison of their biological activity against the natural molecules will be undertaken.

The effect of synthetic PIF and of PRF antagonist upon growth of breast tumor induced by 7,12-dimethylbenzanthracene (DMBA) would then be investigated. Studies of the inactivation and organ distribution of the synthetic peptides will also be performed in view of potential clinical use. The possible role of prolactin in breast cancer and the relatively high frequency of nonpuerperal galactorrhea indicate clearly the importance of gaining knowledge about the nature of the hypothalamic factors regulating PRL secretion. Knowledge of the structure of these substances should permit synthesis of compounds of clinical use.

246. TAMOXIFEN, AN ANTIESTROGEN DRUG FOR BREAST CANCER (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

247. AROMATASE INHIBITORS FOR CONTROL OF BREAST CANCER

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We have prepared compounds which inhibit aromatase (estrogen synthetase) in vitro and have found them to be highly effective in causing regression of DMBA-induced, hormone dependent mammary tumors of the rat. Evidence suggests that aromatase inhibitors act in vivo by inhibiting estrogen biosynthesis: measurements of ovarian secretion were significantly reduced by inhibitor treatment compared to controls and peripheral gonadotropin levels are similar in treated and control rats. Also, when exogenous estradiol was given in addition to inhibitor treatment, tumor regression was prevented. In order to develop aromatase inhibitors as useful compounds for breast cancer therapy and other diseases influenced by estrogen, we propose to investigate further the mechanism of action of aromatase inhibitors. We will determine whether the compounds can inhibit estrogen biosynthesis in vivo by their direct infusion into the externalized ovary of the sheep. We will also determine whether peripheral aromatization can be inhibited in the primate with our present inhibitors. We propose to investigate whether any of the properties of the inhibitors in vivo can be attributed to androgenic activities or whether they can compete for steroid hormone receptors. Using radio-labelled aromatase inhibitors, we are studying the extent of metabolism, distribution and clearance rate of the compounds and whether metabolites contribute to the activity of the inhibitors. By utilizing our structure-activity data we expect to synthesize more potent compounds. An important aspect of our program is the use of affinity labelling and other methods to prepare irreversible inhibitors. We will study the effects of combining aromatase inhibitors with other anticancer agents to determine if more complete and permanent regression can be obtained. We also propose to apply aromatase inhibitors to studying the interrelationships of estrogen with other hormones and their effects on steroid hormone plasma and receptor levels.

248. FLUOROSTEROIDS AS POTENTIAL INHIBITORS OF AROMATASE AND ESTROGEN DEPENDENT MAMMARY TUMORS

Mann, J., Pietrzak, B., University of Reading, Dept. of Chemistry, *Whiteknights, Reading RG6 2AB, England, United Kingdom*

OBJECTIVE: To synthesize some fluoro-analogues of biosynthetic precursors of estrogens, to study their metabolism, and anti-cancer activity, in hope that they will have activity against estrogen-dependent mammary tumors.

APPROACH: The A-ring of readily available steroids, such as androsten-, 17-dione will be modified, usually by the introduction of one or more fluorine atoms. Metabolism studies will be carried out using commercially available microsomes, and biological evaluation will be carried out in collaboration with the Chester Beatty Research Institute, London.

249. PROGRAM IN RADIONUCLIDE STUDIES OF TUMORS AND GROWTH

Spencer, R. P., Hosain, P., Sripada, P. K., Banerjee, S. N., Emran, A., University of Connecticut, Health Center, School of Medicine, Dept. of Nuclear Medicine, *Farmington Ave., Farmington, Connecticut*, 06032, United States of America

The summary for this project is under entry no. 40.

250. EASTERN COOPERATIVE ONCOLOGY GROUP

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The summary for this project is under entry no. 79.

251. ENDOCRINE FACTORS INFLUENCING THE GROWTH OF TUMORS

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The summary for this project is under entry no. 67.

252. ADJUVANT ENDOCRINE THERAPY WITH AN ANTIESTROGEN IN OPERABLE BREAST CANCER PATIENTS ON THE BASIS OF ESTROGEN RECEPTOR ASSAY

Nomura, Y., Yamagata, J., Kondo, H., Kanda, K., National Kyushu Cancer Center, Department of Breast Surgery, *Ohaza-Notame 595, Minami-Ku, Fukuoka 815, Fukuoka, Japan*

The summary for this project is under entry no. 218.

F. OTHER ENDOCRINE THERAPY, WITH OR WITHOUT CHEMOTHERAPY, FOR HUMAN BREAST CANCER

253. ADVANCED BREAST CANCER - AN EVALUATION OF CORTICOSTEROID THERAPY

Minton, M. J., Rubens, R. D., Hayward, J. L., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

For many years additive corticosteroid therapy has been used in this unit to treat advanced breast cancer in elderly women (greater than 65 years) after failed estrogen therapy. A retrospective analysis on 100 patients is now being carried out to evaluate the response to this treatment.

254. THE ANGLO-JAPANESE TRIAL - THE RESPONSE TO ENDOCRINE THERAPY IN GREAT BRITAIN AND JAPAN

Hayward, J. L., Rubens, R. D., Sexton, S., Kumaoka, S., Takatani, O., Yoshida, M., Abe, O., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

This trial was undertaken to compare response to hormone therapy or ovarian ablation in he two countries. Three groups of patients with advanced breast cancer have been compared: a. premenopausal women treated either by oophorectomy or ovarian irradiation; b. women from six months to five years postmenopausal treated with androgen therapy (fluoxymesterone); c. women more than five years postmenopausal -treated with estrogens (stilbestrol).

A review of the results has been carried out biennially in each country by a combined panel of British and Japanese investigators. Entry to both groups was completed in 1977. The final assessment has now been completed and the results are being analyzed. (See ICRF Scientific Report 1977 - report 276; 1978 - report 311.)

255. CONTROL OF NEOPLASTIC GROWTH BY TESTOSTERONE

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OBJECTIVE: To identify defects of regulation that occur in hormone-sensitive and insensitive tumors of prostate and breast.

APPROACH: Variations in the molecular phenotypes of normal and malignant cells are being defined in order to establish whether anomalous growth patterns can be attributed to one or several of the following related factors: (1) Fluctuations in the net concentration of active androgens in the cell; (2) changes in the distribution of androgens between cytoplasm and the nucleus; (3) interactions between androgens, or androgen receptor complexes, and chromatin; (4) hormone-induced temporal variations in the organization and transcription of chromatin. The animal models to be used in the studies are the rat prostate, the transplantable estrogen-dependent rat mammary and prostate carcinomas isolated by Noble. Within certain limits, principles that evolve from the study of animal models will be used as a basis for parallel studies on hyperplastic and neoplastic conditions of human breast and prostate.

PROGRESS: Radioimmunoassays for dihydrotestosterone and testosterone were developed and the concentrations of these androgens in whole-tissue and nuclei were measured during the cycles of growth, regression and regrowth of tumors. The results accumulated to date indicate that under steady-state conditions dihydrotestosterone is localized exclusively in the nucleus while testosterone is confined almost entirely to the cytoplasm. After castration the concentration of testosterone declines more rapidly than that of dihydrotestosterone. Other as yet incomplete results suggest that tumor regrowth is not accompanied by any elevation of the whole-tissue concentration of either androgen.

Screening of human prostatic tissue for phenotypic markers of hormonal sensitivity was also started. In addition to the aforementioned radioimmunoassays, procedures were developed to measure the concentration of nuclear androgen receptor and the activities of the androgen-metabolizing enzymes, 5 alpha-reductase and 3 alpha(beta)-hydroxysteroid dehydrogenase. The results compiled so far are in keeping with the following conclusions: (1) The concentration of androgen receptor is 1000-2000 molecules/nucleus; (2) the nuclear concentration of unbound androgen is 15- to 30-fold greater; and (3) 5 alpha-reductase activity is 10% of normal in carcinoma and 29.0% of normal in hyperplasia.

256. HORMONAL REGULATION OF GROWTH, DIFFERENTIATION AND TUMORIGENESIS OF HUMAN BREAST TISSUES IN VIVO

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OBJECTIVES: A. To define the hormonal requirements for growth of human breast tissues in vitro and in vivo: 1. Organ cultures (explants) of normal human breast tissues will be maintained for 2-4 days in a hormone enriched chemically defined culture media. Growth of the explants will be assessed by 3H-thymidine incorporation into DNA and mitotic figure analysis. 2. Slices of normal human breast tissues will be transplanted to and maintained (1-6 months) in hormone treated athymic 'nude' mice. Growth of the grafts will be assessed by 3H-thymidine incorporation into DNA and mitotic figure analysis. B. To define the hormonal requirements for differentiation (lactation) of human breast tissues in vitro and in vivo: 1. Organ cultures (explants) of normal human breast tissues will be maintained for 4 days in a hormone enriched chemically defined culture media. Differentiation of the explants will be assessed by histological analysis and by alpha-lactalbumin radioimmunoassay. 2. Slices of normal human breast tissues will be transplanted to and maintained (1-6 months) in hormone treated athymic 'nude' mice. Differentiation of the grafts will be assessed by histological analysis and by alpha-lactalbumin radioimmunoassay. C. To induce neoplastic transformation of normal human breast tissues in vitro-in vivo by chemical carcinogens: 1. Organ cultures (explants) of normal human breast tissues will be maintained for 2 days in a carcinogen enriched chemically defined

culture media. After culture, the explants will be removed and transplanted to and maintained (1-12 months) in hormone treated athymic 'nude' mice. Neoplastic transformation of the transplanted human breast tissues will be assessed by periodic palpation and histological analysis of the grafted tissue.

257. PITUITARY AND THYROID FUNCTION IN BREAST CANCER

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The objective of this project is to define the roles played by thyroid hormones and prolactin in the etiology and biology of breast cancer. This goal will be met by studies of nuclear triiodothyronine, cell membrane prolactin, and cytoplasmic estrogen receptors, and mitochondrial alpha-glycerophosphate dehydrogenase in experimental rat mammary carcinomas induced by N-nitrosomethylurea, and human breast cancer tissues. The influence of thyroid function and circulating prolactin levels on the receptor proteins and the thyroid hormone-inducible mitochondrial enzyme will be studied. Clinical investigations will be concerned with the influence of previous drug administration on tumor receptor levels, particular attention being paid to those known to alter plasma prolactin and estrogen levels.

BIBLIOGRAPHIC REFERENCES: Rose, D.P. and Davis, T.E. Plasma triiodothyronine concentrations in breast cancer. Cancer, 43:1434-1438, 1979. Rose, D.P., Pruitt, B., Stauber, P., Erturk, E. and Bryan, G.T. Influence of dosage schedule on the biological characteristics of N-nitrosomethylurea-induced rat mammary tumors. Cancer Res., 40: 235-239, 1979.

258. CONTINUED CLINICALLY ORIENTED STUDIES ON ENDOCRINE THERAPY AND CHEMOTHERAPY OF CANCER

Nordenskjold, B., Radiumhemmet, *S10401 Stockholm, Sweden*

OBJECTIVE: The aim is to further characterize the biology of human mammary carcinoma and lymphomas and to continue our development and evaluation of predictive tests in order to improve curative and palliative treatment of these malignancies.

APPROACH: We have developed methods for measuring DNA synthesis in needle aspirates with 3H-thymidine autoradiography. This technique is used to correlate DNA synthesis with prognosis, histology and response to endocrine therapy and chemotherapy of non-Hodgkin's lymphomas and breast cancer.

We have also developed new technology for measurement of steroid hormone receptors in open biopsies and in needle aspirates from breast cancer and lymphomas. The techniques are based on isoelectric focusing in polyacrylamide gel and are applied to both estrogen and glucocorticoid receptors. The receptor data are correlated to pathology, clinical course and response to endocrine therapy and chemotherapy.

PROGRESS: The initial phase of this work has been published (Nordenskjold et al., Acta Cytologica 20, 137, 1976).

259. THE INFLUENCE OF HORMONE REPLACEMENT THERAPY ON THE INCIDENCE OF BREAST CANCER IN WOMEN

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The demand by women for hormone replacement therapy is increasing. Breast cancer is acknowledged to be hormone-dependent. This is a long-term project to assess the influence of hormone replacement therapy on the incidence of breast cancer in women. A cohort of 300 women is being screened for breast cancer by clinical examination, thermography and mammography before commencing hormone replacement therapy and re-examined at three months and annually thereafter. The control group consists of 300 women matched for age, parity, hormonal status, and family history of breast cancer.

260. THERAPY-INDUCED CHANGES IN HUMAN BREAST CANCER

Panko, W. B., Smith, F. E., Baylor College of Medicine, School of Medicine, Biochemical Oncology Unit, *1200 Moursund Ave., Houston, Texas,* 77025, United States of America

Recent reports suggest that chemotherapy and endocrine therapy are directed at different cell populations within human breast cancer. These reports also suggest that the presence or absence of hormone receptor proteins can indicate the degree of biochemical differentiation of the tumor. The purpose of this study is to determine if endocrine therapy or chemotherapy induces detectable, specific, consistent changes in the degree of biochemical differentiation of human breast cancer as judged by the concentration of estrogen and progesterone receptors. A secondary objective is to determine if the presence, absence or concentration of nuclear estrogen receptor or Type II estrogen receptor is correlated with the results of chemotherapy and/or endocrine therapy. This will be accomplished by the systematic, repetitive analysis of the appropriate receptors in human breast cancer biopsy specimens obtained before endocrine therapy or chemotherapy, and after failure of the therapy or recurrence. Receptors will be determined by single-saturating dose assays using either the sucrose gradient or hydroxyapatite assay methods. A direct fluorescent assay, recently developed, will also be used. Changes in the receptor concentrations or the fraction of estrogen receptor positive cells will be correlated with the type of therapy. Response to the various therapies will be correlated with the concentrations of the appropriate receptors.

261. THE ROLE OF OESTROGEN RECEPTORS IN ADJUVANT ENDOCRINE THERAPY FOR EARLY CANCER OF THE BREAST

Baum, M., University of London, King's College Hospital Medical School, Surgical Unit, *Denmark Hill, London SE5 8RX, England, United Kingdom*

The summary for this project is under entry no. 54.

262. STEROID HORMONE RECEPTOR CONTENT AND PREDICTIVE TEST FOR CHEMOTHERAPY OF BREAST CANCER

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The summary for this project is under entry no. 62.

263. CLINICAL PROGRAM IN BREAST CARCINOMA

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The summary for this project is under entry no. 87.

264. ENDOCRINE FACTORS INFLUENCING THE GROWTH OF TUMORS

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The summary for this project is under entry no. 67.

265. EARLY BREAST CANCER - THE USE OF OVARIAN IRRADIATION AND PREDNISONE AS ADJUNCTIVE THERAPY AFTER MASTECTOMY

Hayward, J. L., Bulbrook, R. D., Meakin, J. W., Allt, W. E., Beale, F. A., Brown, T. C., Bush, R. S., Clark, R. M., Fitzpatrick, P. J., Hawkins, N. W., Jenkin, R. D., Pringle, J. F., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

The summary for this project is under entry no. 197.

266. ENDOCRINE FACTORS INFLUENCING TUMOR GROWTH IN MAN

Pearson, O. H., Manni, A., Brodkey, J., Arafah, B., Case Western Reserve University, School of Medicine, Dept. of Medicine, *2109 Adelbert Rd., Cleveland, Ohio,* 44106, United States of America

The summary for this project is under entry no. 240.

G. ENDOCRINE THERAPY OF BREAST CANCER IN ANIMAL MODELS

267. EFFECT OF AGING ON HORMONAL CONTROL OF MAMMARY TUMORS

Hsueh, A. J., Erickson, G. F., University of California, San Diego Campus, School of Medicine, Dept. of Reproductive Medicine, *P.O. Box 109, La Jolla, California*, 92093, United States of America

The overall objective of the project is to delineate the role of reproductive hormones in the induction and development of spontaneous mammary tumors (SMT) in aging female rats. We plan to correlate the changes in reproductive patterns (and reproductive hormones) with the incidence and growth of spontaneous mammary tumors in order to study the hormonal responsiveness of these tumors. We have studied the hormonal responsiveness of a population of aging female rats bearing spontaneous mammary tumors. Following ovariectomy of tumor-bearing rats, the majority of the SMT in these rats exhibited pronounced decrease in tumor size and subsequent regrowth with a lag period of 1 to 2 months, suggesting hormonal dependency of SMT. A second population of 50 aging female rats has also been maintained to study the effect of hormonal ablation therapies. Histological examination indicated that most of SMT studied are adenofibromas exhibiting varying degrees of secretory activity. In search of a tumor marker for monitoring the possible hormonal regulation of tumor growth, we measured alpha-LA (B protein of lactose synthetase) content in the cytosol fraction (10,000 x g of SMT by a specific radioimmunoassay procedure employing staphylococcus A to precipitate antigen-antibody complexes). High concentration of alpha-LA was found in mammary tissues of lactating rats (21.9 plus or minus 5.6 micrograms/mg protein; mean plus or minus S. E., n equals 6), whereas no alpha-LA was detected in uterus, kidney, fat, heart muscle thymus, and ovary, indicating the tissue specificity of alpha-LA production. In contrast, all 12 SMT examined exhibited varying but significant amounts of alpha-LA. Alpha-LA concentration is greater than 0.1% of the total protein in 66% of the SMT, whereas the remaining SMT have less than 1 microgram alpha-LA/mg protein. These results demonstrate the substantial elevation of alpha-LA in SMT of aging female rats and suggest that alpha-LA may serve as a specific marker for monitoring the hormonal regulation of spontaneous mammary tumorigenesis.

268. RELATIONSHIP BETWEEN HORMONE-DEPENDENT MAMMARY TUMORS AND MAMMARY TUMOR VIRUSES IN MICE

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OBJECTIVE: The objectives of this research program are an investigation of hormone response of mammary tumors induced by mammary tumor viruses from various strains of mice and establishment of transplantable hormone-dependent mammary tumors.

APPROACH: We have succeeded in isolating several transplantable mammary tumors with different hormone responses. These tumor lines are being used for studies on endocrinotherapy with antiestrogenic agents and mechanism of hormonal control of mammary carcinoma with a stress on hormone receptors.

269. MECHANISM OF ANTIHORMONE ACTION IN BREAST CANCER

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Previous studies in this laboratory have focused on the mechanisms of estrogen and prolactin control of breast tumor growth. It is the particular goal of this proposal to investigate the subcellular biochemistry of androgen action in these tumors in order to understand the mechanism by which androgens cause regression of breast cancer tissue. A great deal is known about the early events of androgen action in prostate and other male target tissues. It is generally agreed that testosterone (T) enters the cell and is rapidly converted to dihydrotestosterone (DHT), which then binds to a specific cytoplasmic receptor protein. The steroid complex enters the nucleus, where it presumably acts to stimulate the biochemical chain of events necessary for growth and function. In the genetically determined testicular feminization syndrome described in mice, rats, and humans, it has been proposed that the failure of target organ development is causally related to a lack of the specific cytoplasmic DHT receptor. It is unlikely that androgen-induced regression in breast cancer is mediated by this receptor because of the very large pharmacologic dose requirement.

We are proposing possible mechanisms by which pharmacological androgen administration might result in tumor regression. These proposals will be tested in DMBA-induced rat mammary carcinomas, relating the tumor growth response after androgen treatment to several properties of pre- and post-treatment tumor biopsy specimens.

H. IMMUNOTHERAPY OF BREAST CANCER IN MODEL SYSTEMS

270. CANINE MODEL FOR HUMAN BREAST CANCER IMMUNOTHERAPY

Hurvitz, A. I., Zachrau, R. E., Black, M. M., MacEwen, E. G., Gilbertson, S. R., Animal Medical Center, Dept. of Pathology, *New York, New York, United States of America*

Studies of human breast cancer patients have shown that the biologic behavior of breast cancer reflects an interaction between the aggressive potential of the cancer cells and the tumor-retarding influence of host's tumor-specific cell-mediated immunity (CMI). More recent in vitro studies of leukocytes from human breast cancer patients indicate that simultaneous CMI to autologous breast cancer and the major envelope glycoprotein (gp55) of RIII-murine mammary tumor virus is prognostically beneficial, as judged by postoperative survival characteristics. These findings suggest that gp55 could be of value in immunotherapy and immunoprophylaxis of breast cancer. However, ethical considerations dictate that a test of the therapeutic potential of gp55 be made on an experimental model before clinical trials in humans. The natural behavior and structural characteristics of canine mammary cancer suggest that the dog provides an appropriate model. Preliminary in vitro studies have demonstrated that some breast cancer dogs have CMI to their autologous cancer and/or reactivity to selected human cancers and to gp55. Conversely, some breast cancer patients have CMI to canine mammary carcinomas.

The proposed study will seek to: (1) compare canine and human breast cancers in regard to structural, immunologic and biologic characteristics, and (2) determine whether therapeutic induction of gp55- and/or breast cancer-specific CMI in breast cancer dogs influences the biologic behavior of specifically characterized lesions.

271. EXTRACORPOREAL IMMUNOABSORBENTS FOR IMMUNOTHERAPY OF NEOPLASTIC DISEASE

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This project is designed to continue the assessment of the efficacy of extracorporeal immunoadsorption therapy in treatment of various models of rheumatic and neoplastic diseases in the dog which have now produced promising results. We have developed several immunoadsorbents to which immune reactants have been chemically conjugated or physically entrapped. Each of these immunoadsorbents has been tested extensively in vivo in an extracorporeal circulation system in normal dogs and now in canine hosts with naturally occurring models of human disease, namely systemic lupus erythematosus and adenocarcinoma of the breast. Canine glomerular basement membrane antigen (GBM) has been physically entrapped in a collodion-charcoal immunoadsorbent which has resulted in extraction of circulating GBM antibody and attenuation or arrest of passively induced nephrotoxic glomerulonephritis. Adsorption of circulating porcine specific canine antibodies by extracorporeal perfusion of canine plasma through porcine kidneys has resulted in marked reduction of porcine specific antibodies and permitted the prolonged functional survival of a porcine renal xenograft perfused with whole canine blood. Extracorporeal immunoadsorption over immobilized Staphylococcus aureus -Cowans I has

effected the removal of immune complexes and IgG in dogs with SLE. Similar perfusion of a dog with adenocarcinoma of the breast resulted in a marked gross and histologic regression of substantial tumor mass. C1q has been immobilized in collodion membranes and nylon wool and has demonstrated a capacity to extract immune complexes from the circulation of mongrel dogs. In addition, a chemotherapeutic program has been developed to effect the specific and sustained reduction of antibodies after extracorporeal immunoadsorption. We have now standardized several new radioimmunoassays to measure C1q binding, DNA binding and porcine-specific antibodies in the dog. The objective of the proposed experiments is to continue the longitudinal studies already begun of adenocarcinoma of the breast, SLE and hetrotransplantation with our newly developed immunoadsorbent. These studies will involve careful serological and immunohistochemical assessment of the total disease process. (Text Abridged.)

272. DEVELOPMENTAL THERAPEUTICS OF CANCER

Holland, J. F., Ambinder, E. P., Bekesi, J. G., Bhardwaj, S., Slankard Chahinian, M., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

An integrated program of developmental therapeutics research is proposed that deals with chemotherapy and chemoimmunotherapy in vitro, anti-viral chemotherapy of RNA and DNA viruses, comparative biology of a viral and a chemically induced mammary tumor, a search for the chemical characteristics of hematopoietic micro-environments and an investigation of chemotaxis of monocytes. These areas are supported by highly sophisticated analytical chemical techniques. Mathematical models of tumor growth and its perturbations suggest that empiric associations may be reduced to predictable postulates that could be of great importance in planning therapeutic interventions.

I. IMMUNOTHERAPY AND ADJUVANT IMMUNOTHERAPY OF HUMAN BREAST CANCER

273. THERAPY OF CARCINOMA OF THE BREAST

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The objective of this proposal will be to determine if adjuvant immunotherapy with BCG alone or combination BCG immunotherapy and four drug chemotherapy will increase survival and prolong tumor-free interval in women with Stage II carcinoma of the breast, and to evaluate immunological parameters for following the clinical course and responses to this adjuvant therapy.

274. CHEMOTHERAPY FOR ADVANCED OR METASTATIC CARCINOMA OF THE BREAST

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Regionally advanced and metastatic carcinoma (Ca) of the breast is amenable to a variety of therapeutic modalities. Combination chemotherapy can produce response with improvement in survival. Radiotherapy can provide local control but patients (pts) still die of metastasis. This approach utilizes combination chemotherapy to shrink primary masses and treat overt or micrometastases. Seventeen pts (8 stage III, 9 stage IV) were treated with combination chemotherapy including 5 with inflammatory Ca. After tumor regression, 15 of the 17 underwent surgery, achieving local control. All 5 with inflammatory Ca had elimination of the inflammatory component. A variety of combinations are available for recurrent or metastatic disease, but there are few prospective trials which compare the various treatment regimens and stratify for the prognostic variables. This program randomly compares 3 active regimens for response rates and duration of survival, and evaluates the effect of MER immunotherapy. A group effort is necessary to stratify for the variables. Interim evaluations of the 335 pts entered show that prior postoperative adjuvant radiotherapy is a detrimental factor for determining response. MER immunotherapy also had a detrimental effect upon response rate (p equals .003) and survival was shorter. Further randomization to MER has been discontinued. Interim evaluations of the treatment arms revealed slight but not significant differences among the chemotherapy regimens.

BIBLIOGRAPHIC REFERENCES: Aisner, J.: Breast Cancer. In Wiernik, P.H. (Ed.): The Science and Practice of Clinical Medicine, New York, Grune and Stratton, Inc. 1979 (In press). Aisner, J., Ross, D.D., Wiernik, P.H.: Tamoxifen in advanced male breast cancer. Archives of Internal Medicine 139:480-481, 1979.

275. LEVAMISOLE AS ADJUVANT IMMUNOTHERAPY IN PATIENTS WITH MAMMARY CARCINOMA

Treurniet Donker, A. D., Amery, W. K., Blonk Van der Wijst, J., Bolhuis, R. L., Haije, W., Hop, W. C., Mak, A. C., Rotterdamsch Radiotherapeutisch Instituut, *Grene Hilledijk 301, Box 5201, 3075 EA Rotterdam, Netherlands*

Levamisole, a synthetic immunopotentiator, may have some value in the modulation of host immune resistance in the oncological patient.

This possibility is under investigation in a double-blind prospective randomized clinical trial on patients with mammary carcinoma.

A two-arm trial of levamisole versus placebo is applied to node-positive patients after surgery and radiotherapy for cure have been performed.

A battery of immunological tests is used regularly to monitor the host response during the two-year oral use of this adjuvant immunotherapy.

276. USE OF LIPOSOMES AND OTHER CARRIERS AS VEHICLES FOR THE TRANSPORT OF ANTI-TUMOR COMPOUNDS IN CANCER THERAPY

Ryman, B. E., Barratt, G. M., Charing Cross Hospital, Dept. of Biochemistry, *Fulham Palace Rd., London, W6 8RF, England, United Kingdom*

OBJECTIVE: To use liposomes containing secondary antibodies to clear radiolabelled primary antibodies to tumor products from the circulation of patients when scanning for specific retention in tumors.

APPROACH: Antisera containing the secondary antibodies to human chorionic gonadotrophin and carcinoembyronic antigen will be partially purified. The optimum size and charge of liposome for entrapment will be investigated. Covalent coupling of antibodies to liposomes will also be attempted. Once the antibodies have been shown to be incorporated into liposomes in sufficient concentration, and to be available for antigen binding, they will be tested for their ability to clear primary antibody from the circulation of mice bearing human tumor xenografts.

BIBLIOGRAPHIC REFERENCES: Investigation of the possible tissue distribution and tumor localization of 99m-technetium-labelled liposomes in cancer patients. V.J. Richardson, B.E. Ryman, R.F. Jewkes, K. Jeyasingh, M.H.N. Tattersall, E.S. Newlands and S.B. Kaye, Brit. J. Cancer (1979) 40, 35-43. In vivo distribution of 99mTc-labelled liposomes, K. Jeyasingh, R.F. Jewkes, V.J. Richardson, M.P. Osborne and B.E. Ryman, European Nuclear Medicine Society, Prague, 1979 - Eur. J. Nucl. Med. (1979) 4, 134.

277. POST-SURGICAL COLON AND BREAST CANCER IMMUNOTHERAPY WITH ANTIGEN-RICH PERCHLORIC SOLUBLE TUMORAL EXTRACTS

de Carli, H. O., Restbergs, V., Hospital San Roque, Lab. Oncologia Experimental, *19 y 508 C.C. 350 Gonnet, 1900 La Plata, Argentina*

The summary for this project is under entry no. 220.

278. FOLLOW-UP TECHNIQUE FOR LEVAMISOLE IMMUNOTHERAPY OF POST-SURGICAL COLON AND BREAST CANCER, BY MEANS OF DNCB QUANTITATIVE TEST

de Carli, H. O., Restbergs, V., Hospital San Roque, Lab. Oncologia Experimental, *19 y 508 C.C. 350 Gonnet, 1900 La Plata, Argentina*

The summary for this project is under entry no. 219.

279. AUTOLOGOUS MARROW TRANSPLANTATION

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The summary for this project is under entry no. 206.

280. ADJUVANT RADIO-, CHEMO- AND IMMUNOTHERAPY OF OPERABLE BREAST CANCER

Grohn, P. T., Heinonen, E. O., Klefstrom, P. S., Tarkkanen, J. O., Helsinki University Central Hospital, Dept. of Radiotherapy, *Haartmaninkatu 4, Helsinki, Finland*

The summary for this project is under entry no. 208.

J. CHEMO-IMMUNOTHERAPY OF HUMAN BREAST CANCER

281. CHEMOIMMUNOTHERAPY OF ADVANCED BREAST CANCER

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OBJECTIVES: Determine the efficacy in terms of response, duration of response, and survival of combination chemoimmunotherapy using cyclophosphamide, 5-fluorouracil, Adriamycin and BCG by scarification. Determine the quantitative and qualitative toxicity of the combination. Establish data on immunological status in these patients.

APPROACH: Patients with histologically confirmed carcinoma of breast, stage IV, with progressive disease without known CNS metastasis. Patients will be previously skin tested with DNB and a battery of recall antigens. The dosage schedule is as follows: 5-Fluorouracil - 600 mg/sqm IV day 1; Adriamycin - 50 mg/sqm IV day 1; cyclophosphamide - 600 mg/sqm IV day 1. Repeat cycle at 3 weeks' interval. BCG-C (Fundacao A. de Paiva - Rio Janeiro) 40 mg by scarification days 8 and 15 of each cycle. When the Adriamycin dose of 450 mg/sqm is reached it is discontinued. Methotrexate 50 mg/sqm day 1 and vincristine 1.5 mg/sqm day 1 are added and the therapy is continued for two years if there is no progression. This is a non-randomized study. The protocol has been active since October 1978.

282. ADJUVANT CHEMOIMMUNOTHERAPY IN PRIMARY BREAST CANCER

Senn, H., Jungi, W. F., Amgwerd, R., Kantonsspital St. Gallen, Dept. of Medicine C, *CH9006 St. Gallen, Switzerland*

OBJECTIVES: To determine the influence of a 6-month chemotherapy program followed by BCG for 2 years on recurrence rates, tumor-free interval, survival and certain immune response parameters in primary breast cancer.

APPROACH: Two hundred and fifty-four women with T1-3a, N0-1 (positive or negative), M0 breast cancer were surgically treated by standardized modified radical mastectomy, stratified according to their axillary status into node-negative and -positive subgroups and then randomized to either receive no more treatment than surgical (controls) or receive 6 months of LMF (chlorambucil plus methotrexate plus fluorouracil) followed by monthly BCG-skin-scarifications until recurrence or for 2 years. All patients were examined at least every 3 months with a standardized follow-up program including a skin test battery.

RESULTS: At the last cutoff (June 30, 1978) after 2 1/2 years of median follow-up we observed: 1) A significant reduction in overall recurrence rate in node-negative cases in favor of the LMF/BCG treated subgroup (6.8% vs. 25.4% in surgical controls), 2) a trend, but no statistical difference, towards lower recurrence rates for the LMF/BCG subgroup in node-positive cases (32.2% vs. 45.6% in surgical controls), 3) virtually no reduction of recurrence rate by LMF/BCG in the high risk node-positive premenopausal patients (37.9% vs. 48.4% controls), 4) no difference in survival between adjuvant and control groups in both nodal subgroups at present.

The program continues with detailed follow-up analysis at 6 months.

283. TREATMENT OF METASTATIC BREAST CANCER WITH COMBINATION CHEMOTHERAPY AND BONE MARROW INFUSION

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This is part of a broader project. A summary of this subproject is not available.

284. CALGB PROTOCOL 7682 - COMBINATION CHEMOTHERAPY IMMUNOTHERAPY OF METASTATIC, RECURRENT, OR INOPERABLE CARCINOMA OF THE BREAST

Spaulding, M. B., Henderson, E. S., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

This study compares three combinations of chemotherapy given intermittently until the time of relapse. One patient has been treated at this institution. The patient presented with inoperable inflammatory breast carcinoma. She has had a good response and has been on the protocol for almost one year with complete disappearance of measurable disease. We have noted mild myelo-suppression and have interrupted therapy on several occasions for that reason, but we have had no problems with infection or bleeding secondary to myelo-suppression.

285. C. PARVUM AS A THERAPEUTIC ADJUNCT FOR BREAST CARCINOMA

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This study is designed to improve the results of combined chemotherapy in patients with advanced carcinoma of the breast by the addition of Corynebacterium parvum. The specific objective is to demonstrate that adding Corynebacterium parvum to a combination of cyclophosphamide, methotrexate, 5-fluorouracil, and adriamycin in a group of patients with carcinoma of the breast will: increase response rate; increase response duration; prolong life; decrease the incidence of intercurrent infections; permit greater doses of chemotherapy to be given for a longer time; and augment immunological reactivity.

286. CLINICAL PROGRAM IN BREAST CARCINOMA

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The summary for this project is under entry no. 87.

287. THERAPY OF CARCINOMA OF THE BREAST

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The summary for this project is under entry no. 273.

288. STUDIES OF PATIENTS WITH DISSEMINATED SOLID TUMORS

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The summary for this project is under entry no. 199.

K. OTHER MULTIMODAL THERAPIES OF HUMAN BREAST CANCER

289. MULTIMODALITY THERAPY OF EARLY BREAST CANCER (HUMAN)

Schnipper, L., Beth Israel Hospital, *330 Brookline Ave., Boston, Massachusetts*, 02215, United States of America

This is part of a broader project. A summary of this subproject is not available.

290. THERAPEUTIC TRIAL FOR RAPIDLY PROGRESSING BREAST CANCER IN TUNISIA

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The summary for this project is under entry no. 203.

291. ADJUVANT ENDOCRINE THERAPY WITH AN ANTIESTROGEN IN OPERABLE BREAST CANCER PATIENTS ON THE BASIS OF ESTROGEN RECEPTOR ASSAY

Nomura, Y., Yamagata, J., Kondo, H., Kanda, K., National Kyushu Cancer Center, Department of Breast Surgery, *Ohaza-Notame 595, Minami-Ku, Fukuoka 815, Fukuoka, Japan*

The summary for this project is under entry no. 218.

292. THERAPY OF CARCINOMA OF BREAST

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The summary for this project is under entry no. 211.

L. CHEMOTHERAPY OF BREAST CANCER IN MODEL SYSTEMS

293. CHEMOTHERAPY OF MAMMARY ADENOCARCINOMA IN MICE

Shoemaker, J. P., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1540 Spring Valley Dr., Huntington, West Virginia*, 25701, United States of America

Since the previous report, we have improved our results which have been reported in the Journal of the National Cancer Institute, and in Cancer Research. In two separate experiments, treatment of C3H/He mice bearing transplantable mammary adenocarcinomas (C3HBA) with a regimen of 6-propylthiouracil (PTUra) and 5-fluorouracil (FUra) plus chloroquine phosphate (CP) resulted in complete remissions of 77 and 65% respectively. Treatment with PTUra alone resulted in 41% remissions in experiment 1 and 35% remissions in experiment 2. None of the nontreated control mice in either experiment had spontaneous remissions, and all controls died in each experiment. The principal effect was apparently due to the treatment with PTUra, inasmuch as most of the tumors disappeared during the 21 day treatment period. This observation indicated that the proper timing of the thyroid treatment with PTUra was crucial to achieve the best results. The combined FUra plus CP regimen augmented the effects of the thyroid treatment and resulted in an increase in remissions.

294. MODEL STUDIES FOR ANTI-TUMOR CHEMOTHERAPY

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OBJECTIVE: To obtain more insight into those mechanisms which determine the effectiveness of tumor treatment with cytostatic drugs. Special emphasis will be placed on determining whether the effectiveness of a certain drug treatment in advanced disease can be extrapolated to the treatment of micrometastases with adjuvant chemotherapy.

APPROACH: The effectiveness of a combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and the separate drugs will be compared when the drugs are administered to large flank tumors in mice or their micrometastases. The tumors used are the Lewis lung carcinoma in C57BL/Ka mice which metastasizes to the lung and the mammary carcinoma 2661 in CBA/Raji mice which metastasizes to lymph nodes and/or lung.

PROGRESS: Preliminary results show a more pronounced effectiveness of drug treatment on micrometastases of the Lewis lung carcinoma than of the flank tumors. In contrast, the micrometastases of the 2661 carcinoma respond to a lesser extent to this treatment than the tumors transplanted in the flank.

295. REMISSION OF RAT MAMMARY ADENOCARCINOMAS BY SELECTED DRUGS

Teller, M. N., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

296. CHEMOTHERAPY OF INDUCED RAT MAMMARY ADENOCARCINOMA

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This is part of a broader project. A summary of this subproject is not available.

297. CHEMOTHERAPY-INDUCED ENDOCRINE CHANGES IN BREAST CANCER

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To determine whether the clinically disease-free interval accompanying adjuvant chemotherapy is a result of direct anticancer action, indirect endocrine organ changes, or a combination of both. We intend to approach this problem in three separate ways. We will use a premenopausal patient population exhibiting stage II breast carcinoma, an intact and castrate in vivo model (rat), and two in vitro tissue culture systems: anterior pituitary cells and mammary tumor cells.

298. EFFECT OF ANTIMETABOLITE ON SPONTANEOUS MAMMARY ADENOCARCINOMA OF MICE

Tokuzen, R., Hoshi, A., Kuretani, K., Ministry of Health & Welfare, Pharmacology Div., *5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Tokyo, Japan*

OBJECTIVE: The antitumor effect of 1-hexylcarbamoyl-5-fluorouracil is tested on spontaneous mammary adenocarcinoma of SHN mice with various schedules of oral administration.

APPROACH: The autograft of the tumor is implanted subcutaneously at the site of surgical operation. The compound is administered orally. For the evaluation of the effect of treatments the following three criteria are used: (1) Number of days before the first detection of the local recurrence at the site of operation, (2) postoperative longevity, (3) frequency of lung metastasis as found at autopsy.

PROGRESS: The compound is found to be active not only against transplanted tumors but also against autograft of spontaneous mammary adenocarcinoma.

299. PROTECTION OF MICE FROM DEVELOPING MAMMARY TUMORS BY VACCINATION WITH MTV PROTEINS

Michalides, R. J., Boot, L. M., Ropcke, G., Nederlands Kankerinstituut, Div. of Virology, *108 Sarphatistraat, Amsterdam, Netherlands*

OBJECTIVE: To protect mice from developing mammary tumors, induced by either MTV or hormones, by vaccination with formalin-treated MTV.

APPROACH: Newborn mice at the age of 3-4 weeks are vaccinated with 10 micrograms of formalin-treated MTV and subsequently after one week either infected with MTV, stimulated with hormones by implanting a hypophyseal isograft or not treated at all. The mammary tumor incidence is registered. In addition, blood is taken from these mice once every month by retro-orbital puncture; the presence of antibodies directed against MTV is measured using the MTV-radioimmunoprecipitation (RIP) assay.

PROGRESS: Strains of mice with a low mammary tumor frequency, such as 020 and C57BL, do not possess antibodies directed against MTV. While only some mice of strains with intermediate mammary tumor frequency, such as C3Hf and BALB/c, do possess Ab against MTV, the majority of mice of high mammary tumor strains, such as GR and C3H, possess Ab against MTV. The development of humoral immune response directed against MTV precedes the mammary tumor development. Treating animals with prolactin to increase mammary tumor frequency also increased the proportion of animals carrying Ab against MTV.

300. CORTICOSTEROIDS - CYTOKINETIC AND BIOCHEMICAL STUDIES

Braunschweiger, P. G., Schiffer, L. M., Allegheny General Hospital, Cancer Research Unit, *320 E. North Ave., Pittsburgh, Pennsylvania*, 15212, United States of America

OBJECTIVE: To investigate the effects of synthetic glucocorticosteroids on the growth and cytokinetics of tumor cell populations from a variety of experimental tumor models in mice and rats and correlate these effects with specific glucocorticosteroid receptor levels.

APPROACH: Utilizing a battery of experimental tumor systems in mice and rats, evaluate corticosteroid dose dependent

effects on tumor growth and tumor cell proliferation. Studies will be initiated with methyl prednisolone, dexamethasone and triamcinolone acetonide. Cell kinetic measurements, 3H-TdR labeling index, mitotic index, DNA synthesis time and tumor growth fraction (PDP assay), will be determined prior to and at various intervals after short corticosteroid treatments so that the perturbing effects of these agents on cell proliferation can be evaluated. Sequential chemotherapy schedules with corticosteroids and cycle stage specific agents will be designed and tested to evaluate the therapeutic implications of the corticosteroid induced cell kinetic perturbations. Specific cytoplasmic glucocorticosteroid receptors, determined by the competitive binding dextran charcoal assay, will be evaluated in each model studied and correlated with the effects on tumor growth and cell proliferation. In this way we hope to elucidate relationships between corticosteroid receptor levels, cell proliferation and response to therapy that are not only unique to individual models, but that also have more general applicability to all models.

PROGRESS: In C3H/HeJ spontaneous mammary tumors, in vivo methyl prednisolone (MP, 10 mg/kg q 12 hrs x 3) induces a reversible G1 progression delay. After cessation of treatment, cell proliferation is resumed and characterized by a synchronous movement of cells through the S phase of the cell cycle. Treatment with methotrexate (MTX) or 5-FU was most effective when the sequence interval after MP coincided with maximal S phase cellularity (i.e., when the 3H-TdR LI approached the growth fraction). MTX and 5-FU were least effective when administered at sequence intervals corresponding to times when the 3H-TdR LI was low (Cancer Research 38, 4510-4514 (1978)).

301. REGULATION OF MAMMARY GLAND GROWTH AND REGRESSION

Tang, F. Y., University of Rochester, School of Medicine & Dentistry, Dept. of Obstetrics & Gynecology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

Growth of tumors of the mammary gland can be arrested by ovariectomy in most but not all 7,12-dimethylbenz(alpha)anthracene (DMBA)-induced rat mammary adenocarcinomas. Actual tumor regression in these animals involves production of cyclic adenosine-3',5'-monophosphate (cAMP) and stimulation of cAMP-dependent protein kinase. It has been proposed that a cytoplasmic receptor-kinase (RC) complex is translocated to the nucleus during the initial events leading to tumor regression.

Data from this laboratory have shown that DMBA-induced rat mammary tumors which fail to regress after ovariectomy exhibit an excess of free catalytic (C) subunit activity in their cytosols which is not present in the cytosols of either mammary gland or regressing mammary tumor. The mammary tumors which fail to regress are classified as ovarian hormone independent and exhibit free regulatory (R) subunit activity and a 10-fold lower affinity for cAMP binding than either mammary gland or hormone-dependent (regressing) mammary tumor. Moreover, the hormone-independent mammary tumors fail to accumulate R and C subunit activity in their nuclei. The presence of free R and C subunits in hormone-independent mammary tumor cytosols suggests a failure of an R and C subunit interaction, presumably due to a defective R subunit, which may be necessary for achieving nuclear translocation of the receptor-kinase (RC) complex. In this proposal, we wish to investigate the phenomenon of cytoplasmic 'activation' of the RC complex in regressing rat mammary tumors and determine whether or not cytoplasmic activation of an RC complex may be associated with nuclear accumulation of R and C subunits. Investigation of the occurrence of cytoplasmic receptor activation may provide evidence which may or may not support the concept of nuclear translocation of the receptor-kinase (RC) complex.

302. AN EXPERIMENTAL CANCER CHEMOTHERAPY PROGRAM

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The overall objective of this program is ultimately to provide better chemotherapy for human cancer. To accomplish that objective, a coordinated series of multidisciplinary studies will be conducted as follows: 1) Selected compounds synthesized within our Institute and materials from outside will be tested in established experimental tumor systems and several special models for antitumor activity and in other systems for anti-herpes virus activity. 2) Additional systems, new or new in our laboratory, will be developed and utilized for antitumor tests, such as a rat colon carcinoma, human cancers in nude mice, neurological tumor models and tumors from macrophages, T and B cells. 3) The usefulness of available chemotherapeutic agents will be improved by the development of new combination therapy regimens, including added immunopotentiation. 4) Mechanisms of action studies will be conducted on active compounds and in resistant tumor or leukemia lines. In addition, basic studies with multiple approaches to improve anti-fol therapy will be conducted.

303. CHEMOTHERAPY OF MOUSE MAMMARY PRENEOPLASIAS

Medina, D., Baylor College of Medicine, School of Medicine, Dept. of Cell Biology, *1200 Moursund Ave., Houston, Texas*, 77025, United States of America

This project involves the response of mouse mammary preneoplastic outgrowth lines to a variety of cytostatic drugs currently used in chemotherapeutic regimens for human breast cancer. Previous experiments have demonstrated that some cytostatic drugs can be potent tumor promotors and/or carcinogens. It is the ultimate aim to determine what drugs and drug regimens inhibit both tumor formation and tumor growth.

304. THE ESTABLISHMENT AND CHEMOTHERAPEUTIC RESPONSE OF HUMAN BREAST CANCER XENOGRAFTS IN IMMUNE DEPRIVED MICE

Bailey, M. J., Inst. of Cancer Research, Dept. of Biophysics, *Clifton Ave., Sutton SM2 5PX, Surrey, England, United Kingdom*

OBJECTIVE: To establish a series of transplantable human breast tumor xenografts in immune deprived mice, and to determine the sensitivity of such xenografts to a variety of chemotherapeutic agents both singly and in combination. When this is achieved the xenografts could be used to screen new agents for cytostatic activity against breast tumors, and to assess new combinations of existing agents.

APPROACH: Human breast tumors obtained from operative specimens are implanted into both athymic (nude) mice and mice artificially immune deprived by thymectomy and whole body irradiation. When progressive growth of such implants occurs, serial transplantation to a number of mice is performed, thus developing a stock of tumors for investigation. Each xenograft line so established is then tested in vivo against a variety of drugs, using tumor growth delay as an index of response.

PROGRESS: Eight transplantable xenograft lines have been established. Detailed investigation of sensitivity to cyclophosphamide, methotrexate, 5-fluorouracil, adriamycin, vincristine and melphalan alone and in combination (CMF and AV) has been performed in 4 lines to date.

305. INVESTIGATION OF ESTROGEN-NITROSOUREA CONJUGATES WITH POTENTIAL SPECIFIC ANTITUMOR ACTIVITY

Lam, H. P., Manitoba Inst. of Cell Biology, *700 Bannatyne Ave., Winnipeg, Manitoba*, R3E 0V9, Canada

OBJECTIVE: This project aims to test the hypothesis that specific antitumor activity may be achieved by taking advantage of the presence of receptors with specific binding properties, which might result in selective accumulation of cytotoxic agents in ER-positive mammary tumors.

APPROACH: Some estrogen-nitrosourea conjugates will be synthesized. They will be tested against ER-positive and ER-negative mammary tumor cell lines in vitro and in vivo.

306. EXAMINATION OF THE INTERACTION OF CYTOXIC DRUGS USED FOR THE TREATMENT OF HORMONE DEPENDENT CANCERS WITH STEROID RECEPTOR SYSTEMS

Morris, I. D., University of Manchester, School of Medicine & Dentistry, Dept. of Pharmacology, *Bridgeford St., Manchester M13 9PL, England, United Kingdom*

OBJECTIVE: To investigate whether non-hormonal anticancer drugs will interact with the steroid receptor system in rat and human mammary tumor tissue. To determine whether anticancer drugs induce false negatives in receptor screens.

APPROACH: The effect of two widely used drugs, namely adriamycin and methotrexate, will be investigated. In vivo and in vitro experiments will be conducted and their effects upon the oestrogen and progestogen high affinity receptor system elucidated. The receptor systems in the rat uterus, pituitary and DMBA induced mammary tumor will be examined. In addition, similar experiments will be conducted with human breast tumor tissue. A prospective clinical trial will also determine whether concurrent therapeutic treatment with anticancer drugs effects the results in the breast cancer steroid receptor screen.

307. STEROID SULFURYLATION INHIBITORS AS ANTITUMOR AGENTS

Horwitz, J. P., Brooks, S. C., Zemlicka, J., Rozhin, J., Vaidyanathan, I., Michigan Cancer Foundation, Dept. of Chemistry, *110 E. Warren St., Detroit, Michigan*, 48201, United States of America

The overall objective of the project is the development of novel antitumor agents for use in the treatment of certain human mammary tumors. The aims include the isolation of steroid alcohol sulfotransferase, the synthesis of transition state (multisubstrate) analogs of steroid sulfurylation, the characterization of these analogs in terms of the appropriate steroid sulfotransferase, and evaluation of selected steroid derivatives on dimethylbenzanthracene (DMBA) induced tumors in the rat.

308. RADIOSENSITIZATION BY PLATINUM ANTICANCER COMPOUNDS

Douple, E. B., Richmond, R. C., Simic, M. G., Jennette, K. W., Dartmouth College, School of Medicine, Dept. of Medicine, *P.O. Box 833, Hanover, New Hampshire*, 03755, United States of America

This proposed project is investigating and characterizing the capability of platinum anti-cancer drugs (platinum coordination complexes) to potentiate the therapeutic effects of ionizing radiation on mammalian cells and animal tumors. The parent compound in this family of new drugs, cis-dichlorodiammineplatinum(II), is known to be a potent radiosensitizer of hypoxic bacteria. Results obtained in our laboratory indicate that it should be possible to extend this synergism between the two modalities to tumor cells, confirming a suggestion presented originally by Richmond and Powers.

One objective of this proposed study is to examine the action of a variety of platinum compounds on mammalian cells in culture when used alone or in combination with ionizing radiation. Two cell lines are being used, a mouse mammary adenocarcinoma, MTG-B, and a Chinese hamster lung fibroblast V-79. The cells are treated under various growth conditions, including log phase and plateau phase, and the V-79 cells are also treated in the presence and absence of oxygen using a special gassing apparatus for the production of chronically hypoxic cells.

A second objective is to test for the radiosensitization of hypoxic tumor cells treated in situ. Survival of the transplantable MTG-B cells will be assayed following combined therapy using the tumor latency, TCD50 and TD50 assays in C3H mice. The combined therapy will be studied using a rat brain tumor (gliosarcoma). The brain tumor cells are implanted intracerebrally and tumor growth and host lifespan will be examined following treatment of advanced solid tumors. Results of these studies should identify radiosensitizers and treatment conditions that could improve clinical tumor response.

BIBLIOGRAPHIC REFERENCES: Douple, E.B. and Richmond, R.C. Platinum complexes as radiosensitizers of hypoxic mammalian cells. British Journal of Cancer 37, Suppl. III: 98-102 (1978). Douple, E.B. and Hoeschele, J.D. Effects of radiation and malonato(-)-R,-R- 1,2 - diaminocyclohexaneplatinum(II) on rat brain tumor cells in situ and in culture. Radiation Research 74: 517-518 (1978), Abstract.

309. CELL KINETICS FOR TIMING POSTSURGICAL CHEMOTHERAPY

Schiffer, L. M., Braunschweiger, P. G., Betancourt, S. E., Allegheny-Singer Research Corp., Cancer Biology Section, *320 E. North Ave., Pittsburgh, Pennsylvania*, 15212, United States of America

The summary for this project is under entry no. 191.

310. DEVELOPMENTAL THERAPEUTICS OF CANCER

Holland, J. F., Ambinder, E. P., Bekesi, J. G., Bhardwaj, S., Slankard Chahinian, M., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

The summary for this project is under entry no. 272.

M. CHEMOTHERAPY AND ADJUVANT CHEMOTHERAPY OF HUMAN BREAST CANCER

311. METASTATIC BREAST CANCER TREATED WITH CMF-CF ADRIAMYCIN (HUMAN)

Schnipper, L., Beth Israel Hospital, *330 Brookline Ave., Boston, Massachusetts*, 02215, United States of America

This is part of a broader project. A summary of this subproject is not available.

312. METASTATIC BREAST CANCER TREATED WITH CMF-CF-ADRIAMYCIN

Henderson, I. C., Canellos, G., Frei, E., Wilson, R., Sidney Farber Cancer Center Inc., Division of Medical Oncology, *44 Binney St., Boston, Massachusetts*, 02115, United States of America

OBJECTIVES: 1) To determine if high-dose methotrexate with CF rescue is active in breast cancer. 2) To obtain a complete remission rate with the four-drug combination in excess of 40%. 3) To obtain a median duration of response greater than 12 months. 4) To assess the response of bone lesions in patients with a long duration of response in other sites.

APPROACH: Patient with measurable disease and otherwise eligible for treatment with chemotherpay are treated with a combination of drugs on a 49-day cycle. The patients receive cyclophosphamide 100 mg/sq.m p.o. days 1-14, 5-flourouracil 600 mg/sq.m IV days 1 and 8, methotrexate 3 mg/sq.m IV bolus days 1 and 8, citrovorum factor rescue 10 mg/sq.m IV bolus days 2 and 9, citrovorum factor rescue 10 mg/sq.m p.o. q. 6h. days 2-4 and days 9-11, and adriamycin 70-120 mg/sq.m IV bolus day 29.

PROGRESS: To date 41 patients have been evaluable and the complete plus partial response rate is 73% and the complete response rate is 32%.

313. MEDICAL ADRENALECTOMY WITH AMINOGLUTETHIMIDE IN ADVANCED BREAST AND PROSTATE CANCER

Troner, M. B., Fishman, L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *1201 Northwest 16th St., Miami, Florida*, 33125, United States of America

The purpose of the study was to evaluate the efficacy of medical adrenalectomy with the investigational drug aminoglutethimide in advanced breast and prostate cancer.

Twenty-six patients with metastatic breast cancer who have had prior response to hormonal manipulation were treated. Objective tumor responses were seen in 13 of 26 patients. Responses were seen in soft tissue, bone and pleura. Six of 26 patients had stable disease, and 7 of 26 patients had progression. The median duration of response is 12.8 months. The median survival for the responders is 26 months and that for the non-responders is 5 months. Side effects are minimal and include mild lethargy, rash, fever, and weight gain. This regimen is well tolerated and can be used effectively in metastatic breast cancer. Patients will continue to be added to the study as long as the medication remains in the ivestigational category.

314. PHASE II STUDY OF CHLOROZOTOCIN

Spaulding, M. B., Noyes, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

Chlorozotocin is a new chemotherapeutic agent related to the nitrosoureas. In this study, involving the cooperative group members of the Cancer and Acute Leukemia Group B, the drug is given intravenously every 6 weeks to patients with advanced neoplastic disease in the GI tract, pancreas, lung, or breast, melanoma or lymphoma. The patients in many cases will have received other drugs and will no longer be responsive to them.

Approximately 100 patients have been admitted to this study to date throughout the CALGB associated institutions. Responses have been limited in extent, although of the four patients treated at the Buffalo Veterans Administration Hospital, there has been one good response in a patient with metastatic carcinoma of the colon. The response however was short in duration. There has been no unusual toxicity or problems associated with the use of the drug.

315. CHEMOTHERAPY UTILIZING 5-FU, CYTOXAN AND PREDNISONE

Ahmann, D. L., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

The BCTF has indicated that the major obstacle to curing more patients with breast cancer is the occurrence of systemic metastasis at the time of primary surgery. The addition of chemotherapy, preferably combinations, offers the single best approach to eliminating these microscopic clones. The studies of the Mayo Clinic in advanced disease indicate that this combination causes 50% objective response rate. The experimental data would indicate that more effect should be seen in the earlier aspects of patients' cancer since the growth characteristics would favor more susceptibility. This study combined with our surgical adjuvant study should be complimentary.

316. PRE- AND POSTOPERATIVE CHEMOTHERAPY FOR STAGE II BREAST CANCER

Papaioannou, A. N., Georgoulis, B., Giotis, V., Lysseos, B., Miligos, S., Papadimitriou, G., Vassilaros, S., Evangelismos Medical Center, B Surgical Unit, *24 Ravine St., Athens 140, Greece*

The summary for this project is under entry no. 221.

317. CONTROLLED CLINICAL TRIALS FOR BREAST CANCER AND OTHER TUMORS

Veronesi, U., Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

The summary for this project is under entry no. 213.

318. CHEMOTHERAPY FOR ADVANCED OR METASTATIC CARCINOMA OF THE BREAST

Aisner, J., Wiernik, P. H., Ostrow, S., Van Echo, D. A., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Medical Oncology, *Baltimore, Maryland*, 21201, United States of America

The summary for this project is under entry no. 274.

319. THERAPY OF STAGE II AND STAGE III BREAST CARCINOMA

Scanlon, E. F., Evanston Hospital, *2650 Ridge Ave., Evanston, Illinois*, 60201, United States of America

The summary for this project is under entry no. 212.

320. EFFECT OF INTRAPLEURAL ADMINISTRATON OF ADRIAMYCIN (ADR) IN CARCINOMATOUS PLEURISY

Yoshida, S., Homma, T., Komuro, Y., Nishijima, S., Saitama Cancer Center, Respiratory Division, *818 Komoro, Ina-Machi, Kitaadachi-Gun, Saitama-Ken 362, Japan*

OBJECTIVE: To improve the dismal prognosis of carcinomatous pleurisy.

APPROACH: (1) Twelve patients with malignant involvement of the pleura were treated with intrapleural administration of ADR. Primary sites were 9 lung cancers, 1 breast cancer, 1 fibrosarcoma, and 1 multiple myeloma. Mean plus or minus SD age was 56.5, plus or minus 7.9 years. After the pleural fluid was aspirated as much as possible, ADR in dosis ranging from 10 to 40 mg was instilled into the pleural space once a week. (2) To examine the acute response of pleura to ADR, it was instilled into the pleural space of normal rabbits in concentrations of 0.8 mg/kg, 0.4 mg/kg, and 0.2 mg/kg of body weight.

PROGRESS: (1) Eleven of the 12 patients were cytologically negative in less than 4 weeks after the initial treatment. The cytologic relapses were seen in 4 patients. Mean survival time after the initial treatment was 5.9, plus or minus 5.7 months, and there was a survival of 45.5% at 6 months. There were few side effects in this group. The concentration curve of ADR in pleural fluid in the course of 8 hrs. after the instillation showed 2 patterns which consisted of one compartment and of two compartments which were comprised of a steeper slope immediately after the instillation followed by a gentle slope. More than 20% of ADR instilled remained in the pleural space at 24 hrs. The ADR concentration in serum was less than 0.11 micrograms/ml after the instillation of 40 mg. The amount excreted in urine for 24 hrs. was 7.3, plus or minus 3.1%. (2) There was dose-dependent pleural effusion at autopsies after 1 week. Autopsies after 3 weeks showed much more pleural fluid and moderate fibrinous adhesion in the high concentration group, but little in the low concentration group.

321. ADVANCED BREAST CANCER - A TRIAL TO ASSESS THE CONTRIBUTION OF VINCRISTINE TO ADRIAMYCIN

Rubens, R. D., Sparrow, G. E., Minton, M. J., Sexton, S., Hayward, J. L., Knight, R. K., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

Adriamycin is probably the most effective single agent in the treatment of metastatic breast cancer. Using this drug in combination with vincristine may achieve better results, but this has not been proved in a controlled clincal trial. A major problem with vincristine is the occurrence of neurotoxicity, and this drug also leads to a high incidence of thrombocytosis (Cantwell et al., European Journal of Cancer, 1979, 15, 1065).

Because of these findings and some evidence that vincristine does not contribute to other cytotoxic drug regimens in the treatment of advanced breast cancer, it is of importance to investigate the precise value, if any, of vincristine in combination with Adriamycin in inducing remissions in this disease. It is possible that vincristine may assist indirectly by protecting against thrombocytopenia, and therefore permitting higher, more effective doses of Adriamycin to be given. The aim of this trial is to clarify this situation.

Patients with locally advanced, inoperable or metastatic breast cancer are randomized to receive either Adriamycin alone or in combination with vincristine for a total of eight courses given at three-weekly intervals.

After eight courses, or on progresion of disease, treatment is continued with intermittent cyclophosphamide, methotrexate and 5-fluorouracil.

Assessment of the trial will include objective response rate, duration of remission survival time and treatment toxicity. Entry to this trial was started on May 5, 1977, and at the end of August, 1979, 73 patients had been entered. No results are yet available.

322. SEQUENTIAL IMMUNOLOGIC PROFILE OF CANCER PATIENTS UNDERGOING SURGERY AND ADJUVANT CHEMOTHERAPY

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The summary for this project is under entry no. 134.

323. SYNERGISTIC SEQUENCES OF NUCLEOSIDE DRUGS

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This research emphasizes rational sequencing of chemotherapeutic drugs. Alterations of nucleotide metabolism following drug X are used to exploit drug Y metabolism. Our proposal involves five related research areas.

1. 3-Deazauridine Enhancement of 5-Azacytidine Metabolism and Antitumor Activity: 3-Dau inhibits CTP synthesis. 5-Azacytidine, an analogue of cytidine, is phosphorylated to greater quantities by uridine-cytidine kinase in the absence of CTP, the feedback inhibitor of this enzyme. Consequently more 5-AzaCTP forms, enters RNA, and kills more tumor cells. Preliminary work confirms these effects. Evaluation of human tumor specimens and detailed biochemical studies are planned.

2. MTX Enhancement of 5-FU Metabolism and Antitumor Activity: MTX is synergistic when preceding 5-FU; not because of thymidylate synthetase interactions, but because MTX leads to increased ribonucleotide forms of 5-FU. 5-FUTP is incorporated into RNA in greater quantities and probably accounts for synergistic cell killing. Greater 5-FU phosphorylation is the consequence of increased PRPP availability that occurs following MTX. Elucidation of this interaction is planned. Human

tumor specimens, especially breast and colon, will also be studied.

3. 5-FdUMP Determination by High Pressure Liquid Chromatography: Periodate oxidation degrades ribonucleotides but not deoxynucleotides. Radiolabeled 5-FdUMP formed following (C14) 5-FU treatment of cells is separated by HPLC and quantitated. Our new separation technique allows rapid and quantitative evaluation of changing 5-FdUMP pools. Perturbations of these pools induced by other agents will be performed. Human tumor specimens will also be studied.

4. Enhancement of Other Nucleoside Drug Analogues Requiring PRPP: Azaserine and 6-MMPR increase PRPP pools and augment 5-FU phosphorylation. The nucleoside drugs 6-MP and 6-TG require PRPP for phosphorylation; MTX enhances their metabolism as with 5-FU. Detailed biochemical studies of these drug combinations in animal and human tumors are planned.

5. A Pharmacokinetic Study of High Doses of Ara-C: We are currently using 3gm/m2/12 hr x 4 for leukemia therapy. (Text Abridged.)

324. ADJUVANT CHEMOTHERAPY IN SOLID TÚMORS

Kark, A. E., Pinto, D. J., Harrison, R., Clinical Research Centre, Oncology Unit, *Watford Rd., Harrow, Middlesex, England, United Kingdom*

OBJECTIVE: To test whether adjuvant chemotherapy in early node free and early node involved breast cancer increases the disease free interval and survival following surgery.

APPROACH: Patients with early breast cancer (Tla/b. Nla, MO (Stage I); to. Nlb. MO. - T2b. Nlb. MO (Stage II)) have been entered into one of two trials according to whether they have Stage I or Stage II disease. They have been stratified according to menopausal status: pre-menopausal, including those within 5 years of menopause, and post-menopausal. In each trial patients have been randomized into two groups; those who receive presently accepted treatment of surgery alone ('Petey' mastectomy) and those who receive surgery plus intermittent chemotherapy for 2 years following. The drugs used are melphalan 0.15 mg/kg/day orally for 5 days every 6 weeks. Bone marrow depression is carefully monitored. I.V. vincristine 1 mg is given on day 1 only of each course for a total of 6 courses only. No more is given to avoid any chance of neurotoxicity. Melphalan continues for 2 years. Investigations include 4 ml blood for full blood count every 3 weeks by venepuncture, 35 ml blood for liver biochemistry, hydroxyproline/ creatinine ratio and monitoring of immune response by oncology laboratory every 3 months by venepuncture. CXR every 3 months, ultrasound for possible liver metastases every 3 months, mammography of opposite breast once a year.

PROGRESS: 140 patients have now entered the trial. The median follow-up time is now over 24 months and an interim report is being prepared with regard to resurgence of disease, the place of mammography pre-operatively and the cost-effectiveness of strict follow-up with routine radiological, isotopic and ultrasound investigations.

325. RESERPINE AND BREAST CANCER

Labarthe, D. R., Mayo Foundation, Dept. of Medical Statistics & Epidemiology, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

This is part of a broader project. A summary of this subproject is not available.

326. CANCER CLINICAL RESEARCH

Hickey, R. C., Bodey, G. P., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

This Clinical Research Center Grant has been prepared to serve as a major source of support for the Clinical Research Center which consists of a 22 bed research unit and a 20 bed laminar flow unit. Major divisions of clinical research which will be emphasized include the diagnosis, biology, clinical presentation and the therapy of human cancer. Included are protocols to evaluate cellular kinetics of tumor cells, diagnosis and management of hormone-producing tumors, evaluation of new drugs and drug regimens in malignant diseases, the use of laminar air flow rooms and prophylactic antibiotics in the chemotherapy of leukemia and breast cancer, development of new techniques for study of the immunology of cancer and its immunotherapy, and exploration of the pharmacology of antitumor drugs. Through intradisciplinary research in a specialized setting, it is anticipated that further progress will be made in the management of the cancer patient.

327. PHASE I AND PHASE II STUDIES OF NEW ANTICANCER AGENTS

Woolley, P. V., Georgetown University, School of Medicine, Dept. of Medicine, *3800 Reservoir Rd. N.W., Washington, District of Columbia*, 20007, United States of America

OBJECTIVE: Conduct and complete two Phase I and two Phase II clinical studies per year of new anticancer drugs sponsored by the Division of Cancer Treatment (DCT), National Cancer Institute (NCI). Phase I studies will provide the parameters and characteristics of drug toxicity, the maximally tolerated dose, and, where methods are already available, simple clinical pharmacokinetics of serum and urine drug concentrations. Phase I clinical studies with drug combinations may, on occasion, be performed. Phase II studies will be conducted after the completion of a Phase I study for a specified drug schedule. Phase II studies will provide a statistically significant evaluation of the magnitude of antitumor activity of investigational drugs in one or more of the following diseases and, if applicable, specific subtypes: colorectal carcinoma; carcinoma of the lung; carcinoma of the breast; malignant melanoma; acute leukemia; and malignant lymphoma. In addition, on occasion, drug combinations may be evaluated if warranted by a strong data based rationale.

328. PHASE II STUDIES WITH NEW AGENTS

Van Echo, D. A., Scoltock, M., Aisner, J., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section on Medical Oncology, *Baltimore, Maryland*, 21201, United States of America

Phase II studies are therapeutic investigations of new agents that have undergone Phase I testing (i.e., toxicology and pharmacology studies in humans). Currently, Phase II trials are under way with m-AMSA, an important new agent which has undergone Phase I evaluations (see Z01-CM-06973-01 COB) at our institution. The following diseases are being investigated and have less than 6 patients in each category and therefore valid conclusions cannot be drawn: breast carcinoma, ovarian carcinoma, oat cell carcinoma of the lung, and lymphoma.

329. CIS-DICHLORODIAMMINE PLATINUM II NEUROTOXICITY

Ostrow, S. D., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland*, 21201, United States of America

Cis-dichlorodiammine platinum II (DDP), an investigational antitumor agent in clinical trials since 1972, has antitumor activity in genitourinary neoplasms, lymphomas and breast cancer. Renal, hematologic, gastrointestinal and audiologic toxicities have been seen.

Recently there have been reports of neurologic toxicity, primarily peripheral neuropathy. In patients treated with cisplatinum at doses of 50 to 100 mg/sq.m every three weeks alone or with other chemotherapeutic agents we have observed sensorimotor polyneuropathies of the hands and feet and cases of papilledema, retrobulbar neuritis and normal pressure hydrocephalus.

In some cases, neurologic toxicity has necessitated discontinuance of platinum therapy. Cessation of therapy has resulted in improvement in neurologic symptoms in most cases. Serial nerve conduction studies, prior to and during platinum therapy, have been performed on 10 patients. In 3 patients there has been evidence of a sensory polyneuropathy of axonal type following DDP therapy. Sural nerve biopsy performed on two patients has revealed patterns of axonal degeneration by H and E and electron microscopy studies. However, electron microscopic probe studies and x-ray diffraction analysis have failed to reveal localization of platinum in the nerves.

Continued prospective studies on patients receiving platinum, including neutron activation, detection of platinum and further biochemical and histologic studies on nerve biopsies, are planned.

330. INFLUENCE OF COMBINATION CHEMOTHERAPY ON OVARIAN FUNCTION IN PREMENOPAUSAL PATIENTS TREATED FOR CANCER OF THE BREAST

Brouwers, T. M., Sleijfer, D. T., Willemse, P. H., Rijksuniversiteit te Groningen, City & University Hospital, Dept. of Internal Medicine, *Oostersingel 59, Groningen, Netherlands*

OBJECTIVES: To study the impact of standard adjuvant chemotherapy (CMF) on ovarian function in premenopausal patients and to determine the percentage of patients developing amenorrhea. In the latter group data will be collected to answer the following questions: Does amenorrhea mean that anticonceptive measures are not necessary? Is there still a place for surgical oophorectomy in the hormonal management of metastatic carcinoma in the patient with amenorrhea after adjuvant chemotherapy?

APPROACH: Function of the pituitary-ovarian axis in premenopausal patients before, during and after adjuvant chemotherapy will be assessed by means of weekly determinations of serum levels of oestradiol, progesterone, androstenedione, oestrone, and LH/FSH. Before the start of chemotherapy a LH/RH test will be done if possible in the follicular phase of the ovulatory cycle. If menstrual cycles are absent after completion of chemotherapy the above-mentioned determinations will be done one time in every two months.

PROGRESS: Few patients are analyzed at this time, but it appears that in a large percentage of patients menstrual cycles ceased due to ovarian failure.

331. NEW AGENTS FOR METASTATIC BREAST CANCER (HUMAN)

Kaplan, B. H., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Medicine, *1300 Morris Park Ave., Bronx, New York*, 10461, United States of America

This is part of a broader project. A summary of this subproject is not available.

332. CHEMOTHERAPY AND CHEMOIMMUNOTHERAPY OF CANCER

Holland, J. F., Bekesi, J. G., Bruckner, H., Bhardwaj, S., Cuttner, J., Chahinian, A. P., Slankard Chahinian, M. L., Fernbach, B., Goldsmith, M., Hart, R., Himori, T., Keusch, G., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

In the last calendar year, Program Project Grant (CA15936-05) has been vigorously pursued by the investigators of the Mount Sinai School of Medicine under the Principal Investigatorship of James F. Holland, M.D.

Chemoimmunotherapy of acute myelocytic leukemia continues to provide exciting data.

Research in lung cancer has involved the investigation of a 4-drug combination regimen, MACC plus levamisole, and MACC plus C. parvum.

Our investigation of 4-drug second line chemotherapeutic responses in disseminated breast cancer continues to be productive.

Adriamycin and platinum continue to be the central building blocks for chemotherapeutic regimens in patients with ovarian cancer.

A continuing assessment of our chemotherapeutic regimens in prostatic cancer identifies 15 of 19 responders with six of eight with measurable lesions showing 6% or more regression of the disease. Remaining responders all were characterized by major reduction in pain and reduction in alkaline and acid phosphatase.

Gastrointestinal cancer investigations continue with a central attention to fluorouracil by continuous infusion and intermittent intravenous bolus dosing with mitomycin-C and oral treatment with hexylmethylmelanamine.

Experimental chemotherapy has included active clinical investigation of several new drugs, m-AMSA, maytansine, dichloromethotrexate, L-phosphonoacetyl-l-aspartate (PALA), indocine-n-oxide, and L-alanosine.

In the microbiological research, serum opsonins as the determinant of success in granulocyte transfusions continue under study.

Analytical biochemistry of opportunistic infections has made major progress in identification of D-arabinitol, a metabolite of Candida albicans which can be reproducibly quantified in human serum.

BIBLIOGRAPHIC REFERENCES: Takahashi, I., Ohnuma, T. and Holland, J.F.: Comparison of biological effects of dichloromethotrexate and methotrexate on human leukemia cells in culture. Cancer Res. 39:1264-1268, 1979. Ambinder, E.P., Perloff, M., Ohnuma, T., Biller, H.F. and Holland, J.F.: High dose methotrexate followed by citrovorum factor reversal in patients with advanced cancer. Cancer 43:1177-1182, 1979.

333. ADJUVANT CHEMOTHERAPY AND ENDOCRINE FUNCTION IN BREAST CANCER

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This is part of a broader project. A summary of this subproject is not available.

334. TREATMENT OF METASTATIC BREAST CANCER WITH COMBINATION CHEMOTHERAPY AND BONE MARROW INFUSION

Herzig, G. P., Washington University, School of Medicine, Dept. of Internal Medicine, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

The summary for this project is under entry no. 283.

335. ADJUVANT THERAPY OF EARLY BREAST CANCER

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The summary for this project is under entry no. 198.

336. POSTOPERATIVE PROTRACTED COMBINATION CHEMOTHERAPY VERSUS POSTOPERATIVE RADIOTHERAPY IN AXILLARY POSITIVE LYMPH NODES IN EARLY BREAST CANCER

Patel, D. D., Gujarat Cancer & Research Inst., Dept. of Surgery, *New Civil Hosp. Campus Asarwa, Ahmedabad 380016, Gujarat, India*

The summary for this project is under entry no. 205.

337. EXAMINATION OF THE INTERACTION OF CYTOXIC DRUGS USED FOR THE TREATMENT OF HORMONE DEPENDENT CANCERS WITH STEROID RECEPTOR SYSTEMS

Morris, I. D., University of Manchester, School of Medicine & Dentistry, Dept. of Pharmacology, *Bridgeford St., Manchester M13 9PL, England, United Kingdom*

The summary for this project is under entry no. 306.

338. SWOG 7732, CMF WITH AND WITHOUT TAMOXIFEN IN PATIENTS WITH ESTROGEN RECEPTOR POSITIVE BREAST CANCER, PHASE III STUDY

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

The summary for this project is under entry no. 235.

339. SOUTHWEST ONCOLOGY GROUP PROTOCOL 7809, MAYTANSINE (NSC-153858) THERAPY OF ADVANCED BREAST CANCER, PHASE II

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

This study is designed to treat patients with histologically proven breast cancer resistant to known effective agents and who are expected to survive six weeks. Patients must not be eligible for higher priority protocols and they must have disease progression on prior therapy or have received no hormonal chemotherapy or radiotherapy to the measurable lesion in the last four weeks. Maytansine is a plant extract with demonstrable anti-tumor activity in animals and man. It has many of the side-effects of the vinca-alkaloids. The most severe toxicity is dose related nausea, vomiting, diarrhea, and abdominal cramping. Patients will receive 0.5 mg per m2 per day for 5 consecutive days every 21 days or if the patient has liver metastases or abnormal liver function the dose level will be 0.3 mg per m2 per day for 5 consecutive days every 21 days. The study is designed

to evaluate the effectiveness of maytansine in terms of response rate and survival in patients with breast cancer resistant to standard therapeutic modalities.

No VA patients have been entered on this study to date.

340. SOUTHWEST ONCOLOGY GROUP 7725 - CMPF CHEMOTHERAPY PLUS LEVAMISOLE FOR BREAST CANCER (ABBREV)

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas,* 78284, United States of America

This study is designed to determine the effectiveness of levamisole on the duration of response and survival of patients with advanced breast cancer treated with maintenance chemotherapy. This study is designed to use the continuous Cooper regimen with cytoxan, methotrexate, 5-fluorouracil, vincristine and prednisone as initial cytoreductive treatment for 8 cycles. After a response is observed, maintenance chemotherapy with oral 5-fluorouracil, methotrexate, cyclophosphamide, prednisone in 5 day cycles every 28 days will be instituted. A random half of those patients on maintenance phase of the study will then receive levamisole as an immune adjuvant.

341. PRIMARY BREAST CANCER THERAPY GROUP

Poisson, R. C., Cote, J., Hopital St.-Luc, Surgical Oncological Service, *1058 St. Denis St., Montreal, Quebec,* H2X 3J4, Canada

The summary for this project is under entry no. 207.

342. STUDIES OF PATIENTS WITH DISSEMINATED SOLID TUMORS

Bodey, G. P., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Developmental Therapeutics, *c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

The summary for this project is under entry no. 199.

343. BREAST CARCINOMA

Perloff, M., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York,* 10029, United States of America

This is part of a broader project. A summary of this subproject is not available.

N. OTHER CLINICAL BREAST CANCER TREATMENT STUDIES

344. STUDY ON METHODS OF PREDICTING CHEMOTHERAPY SENSITIVITY

Yuhas, J. M., University of New Mexico, School of Medicine, *University Hill N.E., Albuquerque, New Mexico,* 87131, United States of America

The overall objective is to develop an in vitro means of predicting the response of individual breast cancer patients to chemotherapy. Specifically: development of a battery of rat mammary tumors growing in vitro as multicellular tumor spheroids (MTS); determination of the sensitivity of these tumors to selected drugs both in vivo and in vitro (MTS); performance of initial investigations on the basis of any lack of correlation observed between in vivo and in vitro results; and improvement of our methods for growing MTS directly from breast cancer patient cancer material.

345. CLINICAL TRIALS ON DIFFERENT MODES OF TREATMENTS OF ORAL CANCER, AND CANCER OF THE ESOPHAGUS AND BREAST

Mukherjee, A. K., Medical College Hospitals, Dept. of Radiotherapy & Nuclear Medicine, *Chevayoor Kerala, Calcutta 700073, West Bengal, India*

OBJECTIVES: 1) Clinical trials on treatment of oral cancers of different types by the following three modes of combination treatments: a) chemotherapy in suitable combinations followed by radiotherapy; b) chemotherapy in suitable combinations followed by surgery; and c) chemotherapy in suitable combinations followed by both surgery and radiotherapy. 2) Treatment of cancer of the esophagus with chemotherapy in different combinations followed by radiotherapy. 3) Treatment of cancer of the breast and differential variations of standard modes of treatment at different stages of the disease.

APPROACH: For 1, 2 and 3, different combinations of treatment are given to the patients and their clinical results are being followed up.

PROGRESS: The clinical results are being studied and more data are being collected.

346. PALLIATION OF BREAST CANCER BY LEVODOPA (HUMAN)

Fletcher, W. S., Oregon State Higher Education System, University of Oregon Health Sciences Center, School of Medicine, Dept. of Surgery, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon,* 97201, United States of America

This is part of a broader project. A summary of this subproject is not available.

347. THE EXTRACELLULAR ROLE OF THE PROTEINASE CATHEPSIN B AND OTHER PROTEINASES IN INFILTRATIVE TUMOR GROWTH AND METASTASIS

Poole, A. R., Mort, J. S., Shriners Hospital for Crippled Children, Joint Diseases Laboratory, *1529 Cedar Ave., Montreal, Quebec,* H3G 1A6, Canada

OBJECTIVE: To investigate the role of thiol proteinases in tumor invasiveness and metastasis.

APPROACH: Thiol proteinases and other proteinases are being identified, characterized and purified from tumor fluids, and from explants of human breast carcinomas and mouse mammary tumors. Antibodies to purified thiol proteinases are being used to identify these enzymes. The ability of thiol proteinase to alter cell surfaces and to degrade connective tissue macromolecules, including basement membrane components, is being studied.

PROGRESS: Excessive amounts of a thiol proteinase are selectively secreted from human mammary carcinomas and mouse tumors compared with amounts secreted from non-malignant breast tissue and human fibroadenomas of the breast. This proteinase resembles cathepsin B but is different in that it is stable at neutral pH and does not react with a monospecific antiserum to human liver cathepsin B.

348. MANAGEMENT OF BREAST CANCER (HUMAN)

Ahmann, D. L., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

This is part of a broader project. A summary of this subproject is not available.

349. CARCINOMA OF THE BREAST (HUMAN, MICE)

Eisenfeld, A. J., Yale University, School of Medicine, Dept. of Internal Medicine, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

350. STUDIES OF NATURAL INHIBITORS OF CHEMICAL CARCINOGENS

Reddy, B. S., American Health Foundation Inc., *320 E. 43rd St., New York, New York,* 10017, United States of America

OBJECTIVES: Identify naturally occurring non-toxic materials suitable for addition to normal diets in order to inhibit the development of cancer of the large bowel and breast cancer. Specifically, assess the effects of a variety of dietary fibers on chemically induced colon and breast carcinogenesis in an animal model.

351. CANCER THERAPY - CARCINOMA OF THE BREAST (HUMAN)

Henderson, E. S., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York,* 14263, United States of America

This is part of a broader project. A summary of this subproject is not available.

352. BREAST CANCER STUDY (HUMAN)

Foster, R. S., University of Vermont & State Agricultural College, School of Medicine, Dept. of Surgery, *85 S. Prospect St., Burlington, Vermont,* 05401, United States of America

This is part of a broader project. A summary of this subproject is not available.

353. CANCER CONTROL AND COMMUNITY PHYSICIANS

Fowler, W. C., Begun, J. W., Kaluzny, A. D., Hulka, B. S., Powell, S. P., Pagano, J. S., University of North Carolina, Chapel

Hill Campus, School of Medicine, Dept. of Obstetrics & Gynecology, *Manning Dr., Chapel Hill, North Carolina,* 27514, United States of America

The objective of this project is to improve the clinical management of cancer patients in North Carolina. To accomplish this objective, the proposal combines basic research on the patterns of care provided by physicians in different type practice settings for selected disease sites (breast, cervical and endometrial) and the use of that data to encourage the acceptance of current technology in the clinical care provided cancer patients. The project is considered a demonstration cancer control effort involving a limited geographic area in North Carolina and involving only three disease sites. The project will provide the basis for requesting state funding to develop and maintain an onocologic medical education program. Moreover, the project will provide the basis for developing further studies of the patterns of care involving community physicians throughout the state in cooperation with the Cancer Centers at Duke, Bowman Gray and East Carolina University.

354. CANCER CENTER SUPPORT - COMPREHENSIVE

Carbone, P. P., University of Wisconsin, Madison Campus, Center for the Health Sciences, Dept. of Human Oncology, *500 Lincoln Dr., Madison, Wisconsin,* 53706, United States of America

The Wisconsin Clinical Cancer Center is a University-based comprehensive cancer center dedicated to patient oriented laboratory and clinical cancer research, multidisciplinary care, and professional and public education. The WCC has an academic home in the Medical School and Center for Health Sciences with 45 professional members in the Department of Human Oncology. The Center also serves as a focal point for cancer research and patient care for other departments in the Medical School, providing financial, intellectual, and physical facilities for a large number of associate members. A close relationship exists with these other departments in regard to cancer activities.

The WCCC is responsible for major clinical research programs with multidisciplinary trials for breast, pancreas, lung, melanoma, and genitourinary cancers. Laboratory research programs include etiology, pharmacology, radiobiology, endocrinology, immunology and genetics. Outreach programs include many professional and non-professional educational activities, as well as diagnostic and management networks for colposcopy and head and neck cancer. Future ares of emphasis will include strengthening of current programs, as well as development of new effforts in somatic cell genetics, nutrition and preventive oncology.

355. CANCER CENTER SUPPORT (CORE) GRANT

Holland, J. F., Ambinder, E. P., Bekesi, J. G., Bruckner, H., Bhardwaj, S., Cuttner, J., Slankard Chahinian, M., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York,* 10029, United States of America

The Specialized Cancer Center of Mount Sinai School of Medicine and Hospital coalesces and coordinates research in the general areas of chemotherapy, chemoimmunotherapy, supportive care and biochemical diagnosis. The component research programs deal with laboratory and clinical investigation with particular emphasis on acute lymphocytic leukemia, breast cancer, osteocarcinoma, gastrointestinal cancer, lung cancer, clinical pharmacology, and treatment of viral tumors. The clinical center has 19 research beds. An ambulatory Center for Neoplastic Diseases manages a busy out-patient facility. A core laboratory undertakes analytical studies of drugs and biological materials.

All patients are volunteer participants and informed consent is always obtained.

356. EXPERIMENTAL BASES FOR A MOLECULAR APPROACH TO CANCER PROPHYLAXIS AND THERAPY FOR SOME TYPES OF HUMAN NEOPLASIA

Phillips, L. A., Kang, M. S., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Virus Control Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The ultimate goal of this project is to make possible a molecular approach to cancer prophylaxis and therapy for some types of viral neoplasia, especially human leukemia and cancer of the breast where retrovirus information has been detected. Some of our major findings resulting from our research efforts are as follows: (1) Poly(A), poly(C), and poly(G) sequences are present in all retrovirus RNAs examined. (2) Poly(U) sequences are absent in retrovirus RNA. (3) Poly(C) and poly(G) sequences present in retrovirus RNA are transcribed into complementary poly(dG) sequences and poly(dC) sequences respectively in subunit-length cDNA of retroviruses. (4) The 3'-terminal poly(A) sequences are not transcribed into poly(dT) sequences. (5) Little or no poly(C) and poly(G) sequences have been detected in the cellular nucleic acids examined from nonmalignant mammalian and human embryonic cells. (6) These studies represent a possible molecular approach to cancer prophylaxis and therapy for some types of viral neoplasia, especially human leukemia and cancer of the breast where retrovirus information has been detected.

357. BREAST CANCER PROGRAM

Wittes, R., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

358. CARCINOMA OF THE BREAST (HUMAN)

Montague, E. D., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Radiotherapy, *c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

359. RISK OF MULTICENTRIC IN SITU, INVASIVE CARCINOMA AND AXILLARY NODE METASTASES WITH FOCAL DUCT CARCINOMA OF THE BREAST (ABBREV)

Lagios, M. D., Kempson, R. L., Margolin, F. R., Childrens Hospital of San Francisco, Dept. of Pathology, *3700 California St., Box 3805, San Francisco, California,* 94118, United States of America

The summary for this project is under entry no. 37.

360. MEDICAL ADRENALECTOMY WITH AMINOGLUTETHIMIDE IN ADVANCED BREAST AND PROSTATE CANCER

Troner, M. B., Fishman, L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *1201 Northwest 16th St., Miami, Florida,* 33125, United States of America

The summary for this project is under entry no. 313.

361. CLINICAL TRIAL OF WEIGHT REDUCTION AS AN ADJUVANT IN THE PRIMARY TREATMENT OF BREAST CANCER IN POSTMENOPAUSAL OBESE WOMEN

deWaard, F., Rijskuniversiteit te Utrecht, Inst. of Social Medicine, Dept. of Epidemiology, *Bijhouwerstraat, NL-2501, Utrecht, Netherlands*

The summary for this project is under entry no. 175.

IV. PSYCHOLOGICAL ASPECTS OF BREAST CANCER

362. PSYCHOLOGICAL ASPECTS OF BREAST CANCER

Gates, C. C., Peter Bent Brigham Hospital, *721 Huntington Ave., Boston, Massachusetts,* 02115, United States of America

OBJECTIVES: Bring together the most complete information and most experienced people to solve problems associated with the psychological aspects of breast cancer. Demonstrate how inter-disciplinary groups can work effectively and creatively together on emotional aspects of breast cancer. Disseminate information and implement programs employing demonstrated effective techniques to control emotional morbidity.

363. MENTAL AND SOCIAL PROBLEMS IN BREAST CANCER PATIENTS, AND EFFECTS OF SOCIAL SUPPORT

Levi, L., Wallgren, A., World Health Org., Psychosocial Centre, *S10401 Stockholm, Sweden*

OBJECTIVES: (a) To evaluate benefits and disadvantages, in terms of quality of life and physical, psychological, and social functions, resulting from simple psychosocial support given as an adjuvant to the usual surgical/radiological treatment in patients with cancer of the breast. (b) To study the incidence of psychosomatic, mental, social and economic effects of the primary disease. (c) To study psychophysiological relationships and to identify endocrine, immunological, emotional and/or behavioral 'high risk reactions' (predictors, explainers) to physically, psychologically and/or socially unfavorable processes.

APPROACH: The main investigation includes a controlled study of at least 200 breast cancer patients in the Greater Stockholm region. These patients will be randomly allocated to 2 treatment subgroups and studied on an interdisciplinary basis for a period of two years. Both groups will receive the usual program of care recently adopted by the Department of Oncology. One group will also receive psychosocial support. A sample of women of the same age as the patients but otherwise representative of the women of Greater Stockholm will be sent questions or interviewed in order to establish psychosocial norms with which the patients may be compared.

PROGRESS: The planning and pilot phases will be completed by June 1979. The main investigation will start in July and last three years.

364. AETIOLOGICAL FACTORS IN BREAST CANCER

Alderson, M. R., Greening, W. P., McKenna, J. A., Inst. of Cancer Research, Division of Epidemiology, *Clifton Ave., Sutton SM2 5PX, Surrey, England, United Kingdom*

This project will explore the relationship between history of psychiatric illness, social and emotional adjustment, and exposure and reaction to defined 'life crises' and the relative risk of breast cancer. Women attending an early diagnosis unit will be interviewed and, thus, data will be available on those subsequently found to have breast cancer compared with those with benign and no overt breast lesions. Additional data will be collected from other control patients attending the hospital.

365. WOMEN'S ACCEPTANCE OF BREAST SELF-EXAMINATION

Kegeles, S. S., Grady, K., Lund, A. K., Willms, J., University of Connecticut, Health Center, School of Dental Medicine, Depts. of Behavioral Sciences & Community Health/Psychology, *Farmington Ave., Farmington, Connecticut*, 06032, United States of America

The summary for this project is under entry no. 48.

366. EVALUATION OF COUNSELING FOR MASTECTOMY PATIENTS

Bond, G. R., Blum, L., Visotsky, H., Berlin, N., Oviedo, M., Crivolio, A., Cohen, J., Pomp, H. C., Northwestern University, Chicago Campus, School of Medicine, Dept. of Psychiatry, *303 E. Chicago Ave., Chicago, Illinois*, 60611, United States of America

The summary for this project is under entry no. 217.

367. SYMBOLIC GROUP THERAPY WITH MASTECTOMIZED WOMEN

Fornari, F., Burrone, A., Castaldi, S., Donadoni, M. A., Frontori, L., Marsella, F., Moletta, M., Quintavalle, G., Rutelli, R., Tamburini, M., Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

The summary for this project is under entry no. 215.

V. MEMBER OF BREAST CANCER THERAPY COOPERATIVE GROUPS

368. PRIMARY BREAST CANCER THERAPY GROUP

Frelick, R. W., Ashley, P. F., Whitney, L. W., Ortolani, S., Kyle, A., Wozniak, T. F., Berkowitz, I. M., Samii, S., Tilton, D., Hatfield, D., Ganteaume, K., Fedewa, T. C., Wilmington Medical Center, Section of Oncology, *501 W. 14th St., Wilmington, Delaware*, 19899, United States of America

Current application seeks funding to continue cooperative work within the NSABP over the next five years, starting December 1, 1979. It is anticipated that approximately 25-30 patients per year should be added during that time. Follow-up patients, previously on protocol and added over the next five years would, by the fifth year, number about 170. Past experience with multidisciplinary institutional activities should be enhanced to help stimulate increased understanding and study of improved breast cancer management over the next five years. It is anticipated that the Wilmington group will show increasing activity within the NSABP in developing new protocols and studying the past experiences. Failure to accrue more patients to Protocol VI demonstrates the need for continued education of the medical and surgical staffs, although they have participated in our cooperative efforts to collect appropriate biological material and data from their patients in special projects of the NSABP.

We are contributing data from patients entered into the various group protocols as a participating institution in the Primary Breast Cancer Therapy Group. The present application seeks funding (a) to permit continued patient accrual in ongoing protocols, (b) to continue follow-up of patients entered into protocols which have terminated, (c) to collect appropriate biological material and information relevant to such protocols, and (d) to enhance the multidisciplinary approach of this institution in clinical trials. This application seeks continuation of the above. Case accrual from the Wilmington Medical Center to the National Surgical Adjuvant Breast Program started with Protocol V, as a cooperating investigator, through the Central Oncology Group. Initial contract funding was changed to a grant on 4/1/77, and extended to November 30, 1979.

369. PRIMARY BREAST CANCER THERAPY GROUP

Wallack, M. K., Butcher, H. R., Bauer, W. C., Perez, C. A., Ratkin, G., Washington University, School of Medicine, Dept. of Surgery, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

Washington University School of Medicine will participate in studies of the National Surgical Adjuvant Breast Project which will be described in detail in the Headquarters grant application from the University of Pittsburgh. Briefly, these are cooperative, inter-disciplinary, clinical breast and colon cancer studies utilizing surgery, chemotherapy, radiotherapy and immunotherapy and combination of these modalities. The methods used will be those approved for cooperative group studies and will include standard techniques of diagnosis, treatment, and laboratory studies used in the management of solid tumors. The cumulative data base devised from these studies is expected to aid in predicting the results of conventional therapy for the tumors studied by the participating institutions. The ultimate goal of this research is to improve the longevity of adults with carcinoma of the breast and carcinoma of the colon and rectum. The group at Washington University School of Medicine has been reorganized to obtain the necessary patients to help generate this data.

370. PRIMARY BREAST CANCER THERAPY GROUP

Fisher, B., Deutsch, M., Fisher, E. R., Jacobs, S. A., Wolmark, N., University of Pittsburgh, School of Medicine, Dept. of Surgery, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

The University of Pittsburgh was one of the founding institutions of the Primary Breast Cancer Therapy Group (NSABP) in 1958 and has continued uninterrupted as a major participant and contributor to the various group protocols. Patients (450) have been entered into protocols evaluating the relative efficacy of radical and total mastectomy with and without postoperative radiation, segmental mastectomy and a variety of protocols employing chemotherapy in various combinations alone or with the antiestrogen tamoxifen or C. parvum. Since all patients had Stage I or II breast cancer and received prolonged adjuvant therapy, protracted intensive follow-up continues to be involved. For example, in Protocol No. B-04 into which 200 patients were entered 70% of patients are still being followed despite the fact that the average time on study is almost 6 years. In addition to entering patients into protocols and providing the

NSABP Headquarters with high quality data, this institution has been instrumental in providing patients and material for carrying out biological and ancillary studies generated by protocol findings. For example, a Phase I study was carried out entirely at this institution to obtain additional information relative to dosages of CP in humans and more exact information on the toxicities which occur following administration of this agent. In another investigation utilizing serum samples from patients in this institution it was found that there was a lack of association of disease-free survival following adjuvant chemotherapy with depression of ovarian function. More recently, we have carried out a pilot study at this institution to evaluate the mutagenic effects of cytostatic drugs on human lymphocytes. The present application seeks funding (a) to continue to follow patients who have been entered into protocols which have been terminated, (b) to permit patient accrual in ongoing protocols, (c) to participate in the design of new protocols and the accrual of patients in new protocols, and (d) to collect appropriate biological material and information relevant to such protocols. Finally, this proposal provides the single most important mechanism for promoting the multidisciplinary treatment of cancer via clinical trials in this environment.

371. PRIMARY BREAST CANCER THERAPY GROUP

Pilch, Y. H., Orloff, M. J., Saltzstein, S., Mendelsohn, J., Utley, J. F., Barone, R. M., University of California, San Diego Campus, School of Medicine, Dept. of Surgery, *P.O. Box 109, La Jolla, California*, 92093, United States of America

As a participating institution in the Primary Breast Cancer Therapy Group (NSABP), we are contributing data from patients entered into Protocol Nos. 4,6,8,9,10 of the group. The present application seeks funding (a) to permit continued patient accrual in ongoing protocols (Nos. 6,9 and 10), (b) to continue follow-up of patients entered into protocols which have terminated (Nos. 4 and 8), and (c) to collect appropriate biological material and information relevant to such protocols. The ongoing protocols are: (1) No.6: A trial to compare the worth of segmental mastectomy with and without breast radiation with total mastectomy plus axillary dissection. All patients will undergo axillary dissection and those with histologically positive axillary nodes will receive adjuvant chemotherapy. (2) No. 9: A trial to determine whether the anti-estrogen Tamoxifen when combined with chemotherapy improves the results obtained with chemotherapy alone in the adjuvant therapy of Stage II breast cancer. (3) No. 10: A trial to compare the value of the immunopotentiator C. parvum combined with chemotherapy vs. chemotherapy alone in the adjuvant therapy of Stage II breast cancer. We will participate in new NSABP protocols now being designed, e.g., an adjuvant therapy protocol for breast cancer patients with negative axillary nodes and a protocol to evaluate various treatment modalities in the management of patients with Stage III breast cancer.

372. PRIMARY BREAST CANCER THERAPY GROUP (NSABP)

Glass, A. G., Hayes, N., Erwin, M., Bach, R., McFarland, R., Trautman, P., Chan, T. T., Molendyk, J., Willis, N., Kaiser Foundation Research Inst., *1956 Webster St., Room 310 B, Oakland, California*, 94612, United States of America

The NSABP is a multi-institution cooperative group studying the efficacy of various treatment plans for cancers of the breast and bowel. The Kaiser-Permanente Medical Care Program, Portland, Oregon, has been a member of the NSABP for five years, first under a contract and subsequently as a granted institution. Our accrual of patients has steadily increased as the Kaiser Health Plan population has grown and as we have involved more and more surgeons in NSABP activities. Over the next five years, the term of this grant renewal, we expect the number of patients available for study to increase by close to 50% as our Plan membership rises.

The basic organization of our group includes the principal investigator, a medical oncologist, who oversees a core team of nurse oncologists, an administrator and a counselor. Patients are quickly identified from nearly automatic referral by surgeons after the initial diagnostic maneuver has been performed. Patients are then interviewed and randomized into the appropriate study. All therapy is carried out at a single central location. Records are filed in the same location, providing both quick access to pertinent information and assurance of excellent follow-up. Over the next five years this basic system will remain intact but will need to expand somewhat as more patients are added to study.

The principal investigator is Chairman of the Chemotherapy Committee of the NSABP, and, as such, is frequently involved in Headquarters activities both by phone and on frequent trips to Pittsburgh. He will continue his major involvement with protocol design, toxicity monitoring and general assistance to investigators with management of patients on study.

373. PRIMARY BREAST CANCER THERAPY GROUP (NSABP) HEADQUARTERS

Fisher, B., Redmond, C. K., Fisher, E. R., Deutsch, M., Stoller, R., Wolmark, N., University of Pittsburgh, School of Medicine, Dept. of Surgery, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

The Primary Breast Cancer Therapy Group (NSABP) was originally established in 1958 and presently has 80 nurse/data managers and 421 investigators of record. The latter consist of surgical, medical, endocrinologic, radiologic oncologists as well as pathologists and immunologists, emphasizing our multidisciplinary nature. The NSABP objectives are (a) to assess the worth of new and promising therapies when employed either alone or in concert with other modalities, (b) to allow for evaluation of the worth of modalities presently employed when used in innovative ways to test current biological hypotheses (c) to obtain biological and other pertinent data so as to better understand the natural history of patients with breast cancer permitting the formulation of better treatment strategies and (d) to enhance the quality of care of breast cancer patients by educating physicians to the findings and experiences of this group.

Since 8/71 when Protocol B-04 was begun, six additional protocols were implemented to evaluate therapy in Stages I and II breast cancer. Almost 5000 eligible patients have been accrued and as of 12/78, 3916 (83%) were still alive and being followed. Over 1000 patients were still actively receiving protocol prescribed chemotherapy. During 1978 those patients generated approximately 50,000 forms and materials which required processing by the Statistical Unit. The present application is submitted so that efforts toward fulfilling the above documented objectives may be continued. More specifically, the aims are to (1) continue follow-up on all patients entered into NSABP protocols relative to treatment failure and survival, (2) complete patient entry on three ongoing protocols, (3) design and implement analyses of data obtained on all protocols relative to end results, acute and long-term toxicities, pathological and clinical discriminants and correlations, and biological measurements. These analyses will use multivariate techniques. Additional aims are (4) to develop and implement statistical methodology associated with cross-protocol comparisons, (5) implement appropriate biological investigations and (6) continue and extend quality control procedures to ensure the integrity of the treatment(s) administered and the validity of the long-term therapeutic results.

374. PRIMARY BREAST CANCER THERAPY GROUP

Margolese, R. G., Lachance, C., Guerra, J., Wainberg, M., Small, P., Jewish General Hospital, Tumor Clinic, *3755 Cote St. Catherine Rd., Montreal, Quebec*, H3T 1E2, Canada

Information obtained by retrospective analysis of cases not initially managed to provide quality data is of limited use in forming a basis for valid conclusions. This research group, through the use of the prospective randomized clinical trial is attempting to apply the scientific method to the solution of clinical problems in primary breast cancer. As a participating institution in the NSABP we have contributed, and are continuing to contribute data from patients entered into the various group protocols. We have made a major contribution to Protocol 4, a comparison of radical mastectomy versus total mastectomy with radiation vs. total mastectomy alone. As follow-up data continued to indicate the validity of the original hypothesis that there was no significant influence of treatment on disease-free interval or survival, a second surgical prospective trial was undertaken to evaluate segmental mastectomy with and without breast radiation vs. total mastectomy. All patients with positive axillary nodes receive a standard 2 drug chemotherapy. Patients

have also been entered into adjuvant chemotherapy protocols, specifically Protocol No.5: L-PAM vs. Placebo; No.7: L-PAM vs. L-PAM and 5FU; No.8: L-PAM and 5FU vs. L-PAM, 5FU and Methotrexate; No.10: L-PAM and 5FU vs. L-PAM, 5FU and C. parvum, No.9: L-PAM and 5FU vs. L-PAM, 5FU and Tamoxifen. Thus, data will be obtained prospectively to evaluate the efficacy of 1 vs. 2 vs. 3 drugs involving chemo, hormonal and immunotherapeutic combinations giving information on the value and toxicity of multi-modality combination therapy. This application renewal seeks funding to a) permit continued patient accrual in ongoing protocols, b) to continue follow-up of patients already entered, and c) to collect pertinent biological material and information relevant to such protocols. The aim of this proposal is to continue to develop these kinds of data, enhancing the multi-disciplinary approach of this institution through clinical trials to obtain meaningful information in planning the primary therapy of breast cancer.

375. PRIMARY BREAST CANCER THERAPY GROUP

Shibata, H. R., Himal, H., Tremblay, G., Guerra, J., Dorval, G., Knaack, J., Royal Victoria Hospital, *687 Pine Ave. W., Zone 2, Montreal, Quebec, Canada*

The NSABP as a research group has shown by the use of the prospective randomized clinical trial that: 1) Local therapy as indicated by Protocol B-04, a comparison of radical mastectomy versus total mastectomy versus total mastectomy with post-operative irradiation has no significant influence on disease-free interval or survival. 2) Adjuvant therapy as indicated by Protocol B-05, a comparison of L-PAM versus placebo in histologically proven Stage II patients has significantly prolonged the disease-free interval and survival in a subset of women, 19 years or younger.

As a participating institution in NSABP, we have made and will continue to make major contributions to: 1) Protocol B-06, which is designed to determine whether local therapy in the form of total mastectomy or segmental mastectomy plus breast irradiation is comparable to segmental mastectomy. All patients will undergo axillary node dissection and those with metastatic nodes will receive two drugs, L-PAM and 5FU as adjuvant therapy. 2) Protocols B-07 (L-PAM vs. L-PAM and 5FU), B-08, (L-PAM and 5FU vs. L-PAM and 5FU and methotrexate) and B-09 (L-PAM and 5FU vs. L-PAM and 5FU and tamoxifen). These protocols are designed to determine whether combination adjuvant therapy can further improve the disease-free period and survival involving chemotherapy and anti-estrogen hormonal therapy.

This institution seeks further funding to continue: 1) Accrual of patients in ongoing clinical trials, 2) close follow-up of patients already entered into above protocols, 3) to obtain information and specimens relevant to these trials, 4) collaborative studies with other researchers, and 5) input into new protocols.

The basic purpose of this proposal is to attempt to improve the disease-free interval and survival of the women with breast cancer by the multi-disciplinary approach and secondarily to educate medical students and colleagues in practice that the prospective randomized clinical trial is the best way to obtain sound and meaningful data.

376. PRIMARY BREAST CANCER THERAPY GROUP

Fisher, B., University of Pittsburgh, School of Medicine, Dept. of Surgery, *3550 Terrace St., Pittsburgh, Pennsylvania,* 15261, United States of America

OBJECTIVES: Continue follow-up on all patients entered into protocols relative to treatment failure and survival. Complete patient entry on three ongoing protocols. Design and implement analyses of data obtained on all protocols relative to end results, acute and long-term toxicities, pathological and clinical discriminants and correlations, and biological measurements. Develop and implement statistical methodology associated with cross-protocol comparisons. Implement appropriate biological investigations. Continue and extend quality control procedures to ensure the integrity of the treatment(s) administered and the validity of the long-term therapeutic results.

377. ADJUVANT PRIMARY BREAST CANCER THERAPY GROUP

Deckers, P. J., Prendergast, M., University Hospital Inc., Depts. of Surgery/Surgical Oncology, *75 E. Newton St., Boston, Massachusetts,* 02118, United States of America

Boston University Medical Center (University Hospital and Boston City Hospital) is currently engaged in the following clinical trials of the National Surgical Adjuvant Breast and Bowel Project. B06: A protocol to compare segmental mastectomy and axillary dissection, with and without radiation of the breast, and total mastectomy and axillary dissection. (After surgery, any women with 1 or more positive axillary nodes receives 17 cycles of chemotherapy with L-PAM, 4 mg/m2 PO and 5-FU, 300 mg/m2 IV dialy X 5 every 6 weeks). B09: A clinical trial to compare combination chemotherapy with and without Tamoxifen in the management of patients with surgically 'curable' breast cancer who have one or more positive axillary nodes. Chemotherapy is given as outlined above in B06. Tamoxifen is given at a dose of 10 mg BID. C01: A clinical trial to evaluate post-operative systemic chemotherapy and post-operative immunotherapy in the management of colon carcinoma. Patients who have Duke's B or Duke's C adenocarcinoma of the colon are randomized to surgery alone, chemotherapy consisting of MeCCNU 130 mg/m2 PO Day 1; 5-FU 325 mg/m2 IV Day 1 through 5; 5-FU 375 mg/m2 IV Day 36 through 40 and Vincristine 1 mg/m2 Day 1 and 36 or to immunotherapy with BCG (Bacillus Calmette-Guerin - lyophilized Pasteur). Dose is 6 times 10 to the 8th power viable organisms given by scarification weekly X 12, then every other week for 1 1/2 years. R01: A clinical trial to evaluate post-operative radiation and post-operative systemic chemotherapy in the management of resectable rectal carcinoma. Randomization is to surgery alone, post-operative radiation to the entire pelvis including the perineum, or to systemic chemotherapy given as outlined above in C01.

BIBLIOGRAPHIC REFERENCES: Wang, B.S., Deckers, P.J. and Mannick, J.S.: Kinetics of the transfer of tumor-specific cytotoxicity with immune RNA. Clinical Immunol. and Immunopathol. 9:218-228, 1978. Leong, S.P.L., Cooperband, S.R., Deckers, P.J., Sutherland, C.M., Cesare, J.F. and Krementz, E.T.: Antibody-induced movement of a common melanoma membrane antigen(s) on the surface of unfixed human melanoma cells. Cancer Research, 39:2125-2131, June, 1979.

378. PRIMARY BREAST CANCER THERAPY GROUP (NSABP)

Aust, J. B., Cruz, A. B., Bannayan, G. A., Mira, J. G., Livingston, R. B., Thor, D. E., Reed, R. C., University of Texas, Health Science Center at San Antonio, South Texas Medical School, Dept. of Surgery, *7703 Floyd Curl Dr., San Antonio, Texas,* 78284, United States of America

This institution continues to contribute data gathered from patients who were entered into the various protocols generated by the NSABP in the past several years. A significant number of patients was entered in NSABP Protocol No. 4 which evaluated radical mastectomy and total mastectomy with radiation, and total mastectomy alone in patients with clinically negative axillary nodes; radical mastectomy and total mastectomy with radiation in patients with clinically positive axillary nodes. Patients with positive axillary nodes were also entered into Protocol No. 7 evaluating L-PAM with L-PAM plus 5-FU, and Procotol No. 8 - L-PAM plus 5-FU plus methotrexate versus L-PAM plus 5-FU. All of these protocols are already closed to patient accrual but follow-up studies are ongoing. This institution is continuing to enter patients into Protocol No. 9, a trial to determine whether the antiestrogen tamoxifen when combined with chemotherapy improves the results obtained with chemotherapy alone. As soon as the required patient accrual is reached in this protocol, patients will be entered into the remaining breast protocols that are still open, namely No. 6, comparing segmental mastectomy with and without breast radiation with total mastectomy plus axillary dissection; and No. 10 to compare the value of immunopotentiator C. parvum combined with chemotherapy versus chemotherapy alone. A protocol to evaluate various treatment modalities in management of Stage III breast carcinoma is being finalized. We have started to participate in the newly opened randomized objective adjuvant therapy of colorectal carcinoma.

In summary, the aim of this program is to enhance the multidisciplinary approach to the treatment of cancer in clinical trials designed to improve care and survival rates. We are, therefore, applying for renewal of grant funding to (a) permit continued patient accrual in ongoing protocols, (b) continue

follow-up of patients entered into protocols which have been closed, and (c) collect appropriate biological material and information relevant to such protocols.

379. PRIMARY BREAST CANCER THERAPY GROUP (NSABP)

Cohn, I., Louisiana State University, Medical Center, School of Medicine, Dept. of Surgery, *1542 Tulane Ave., New Orleans, Louisiana*, 70112, United States of America

OBJECTIVE: To evaluate the clinical effects of adjuvant chemotherapy following surgery for stage II breast cancer. Specifically, to determine the efficacy of L-PAM and 5-FU, as compared to L-PAM, 5-FU, tamoxifen in the adjuvant management of post-surgical patients with positive lymph nodes.

380. PRIMARY BREAST CANCER THERAPY GROUP (NSABP)

Gardner, B., Rosenthal, J., State University of New York, Downstate Medical Center, School of Medicine, Dept. of Surgery, *450 Clarkson Ave., Brooklyn, New York*, 11203, United States of America

As a participating institution in the Primary Breast Cancer Therapy Group (NSABP), we are contributing data from patients entered into the various group protocols. We have made a major contribution to Protocol 4, which is a protocol to evaluate the relative efficacy of radical mastectomy alone in patients with clinically negative axillary nodes. A comparison between radical mastectomy and total mastectomy with radiation is also made in those with positive axillary nodes. Patients have also been entered into Protocol 5, which compares L-PAM and Placebo and Protocol 6 which evaluates L-PAM with L-PAM plus 5-FU. The present application seeks funding: (a) to permit continued patient accrual in ongoing protocols, (b) to continue follow-up of patients entered into protocols which have terminated, and (c) to collect appropriate biological material and information relevant to such protocols. The new protocols are: (1) No. 6: A trial to compare the worth of segmental mastectomy with and without breast radiation with total mastectomy plus axillary dissection. All patients will undergo axillary dissection and those with histologically positive axillary nodes will receive adjuvant chemotherapy. (2) No. 8: A trial to compare the worth of three-drug chemotherapy (L-PAM, 5-FU and methotrexate) with two-drug chemotherapy (L-PAM, 5-FU). (3) No. 9: A trial to determine whether the antiestrogen tamoxifen when combined with chemotherapy improves the results obtained with chemotherapy alone. (4) No.10: A trial to compare the value of the immunopotentiator C. parvum combined with chemotherapy vs. chemotherapy alone. (5) No. 11: A trial to evaluate various treatment modalities in the management of patients with Clinical Stage III breast cancer. In addition, the NSABP membership has decided, because of its unique composition, to implement adjuvant protocols for primary colorectal carcinoma. The group has the same capability to accomplish this as it has done for breast cancer. This institution will participate in such protocols. Finally, another aim of this proposal is to enhance the multidisciplinary approach of this institution in clinical trials.

381. PRIMARY BREAST CANCER THERAPY GROUP (NSABP)

Jochimsen, P. R., University of Iowa, School of Medicine, Dept. of Surgery, *Jessup Hall, Iowa City, Iowa*, 52240, United States of America

As a participating institution in the Primary Breast Cancer Therapy Group (NSABP), we contribute data from patients entered into various group protocols. We have made a major contribution to protocol No. 4, which is a protocol to evaluate the relative efficacy of radical mastectomy and total mastectomy with radiation and total mastectomy alone in patients with clinically negative axillary nodes. A comparison between radical mastectomy and total mastectomy with radiation is also made in those with positive ancillary nodes. Patients have also been entered into protocol No. 7A, which evaluates L-PAM vs. L-PAM plus 5-FU and protocol No. B-08, which is a trial to compare the worth of L-PAM plus 5-FU plus methotrexate vs. L-PAM plus 5-FU. The present application seeks funding: (a) to permit continued patient accrual in ongoing protocols, (b) to continue follow-up of patients entered into protocols which have terminated, and (c) to collect appropriate biological material and information relevant to such protocols. The new protocols are: (1) protocol No. B-09: a trial to determine whether the antiestrogen tamoxifen, when combined with chemotherapy, improves the results obtained with chemotherapy alone; and (2) protocol No. B-10: a trial to compare the value of the immunopotentiator C. parvum combined with chemotherapy vs. chemotherapy alone. In addition, the NSABP membership has decided, because of its unique composition, to implement adjuvant protocols for primary colonic and rectal carcinomas. The group has the same capability to accomplish this as it has done for breast cancer. This institution will participate in such protocols. Finally, another aim of this proposal is to enhance the multidisciplinary approach of this institution in clinical trials.

382. PRIMARY BREAST CANCER THERAPY GROUP (NSABP)

State, D., Eisert, D., Hirose, F. M., Shabot, M. M., Schick, P., Los Angeles County Harbor General Hospital, Dept. of Surgery, *1000 W. Carson St., Torrance, California*, 90509, United States of America

The work for this year will entail attempting to find effective adjuvant therapy for patients with Stage II breast cancer. In addition, an attempt to ascertain whether in patients with Stage O and Stage I lesions smaller than 2 cm, a partial mastectomy is satisfactory surgical therapy. This should entail placing 20-25 more patients on existing NSABP protocols. In addition, the 83 patients already on NSABP protocols will continue to be followed.

383. PRIMARY BREAST CANCER THERAPY GROUP (NSABP)

Lawrence, W., Belgrad, R., Diasio, R. B., Kay, S., Terz, J. J., Horsley, J. S., Satterwhite, B., Virginia Commonwealth University, Medical College of Virginia, Dept. of Surgery, *1200 E. Broad St., Richmond, Virginia*, 23298, United States of America

The Division of Surgical Oncology of the Medical College of Virginia Cancer Center will continue to participate in the Adjuvant Chemotherapy Protocol for Breast Cancer and Colorectal Cancer of this cooperative group. This institution has been a participant in this project since 1971 and has entered 105 patients in the various protocol to date. Currently, the Adjuvant Chemotherapy Clinic of the Joint Cancer Clinics of the Medical College of Virginia are following 87 patients who have been entered on various protocol. We plan to continue to follow previously entered patients and to continue to enter new patients in adjuvant chemotherapy protocol for both breast cancer and colorectal cancer.

384. PRIMARY BREAST CANCER THERAPY (NSABP)

Dimitrov, N. V., Rice, W. T., Koucky, C., Knapp, W., Young, J., Aabo, K., Saginaw Cooperative Hospitals, Dept. of Medicine, *830 S. Jefferson Ave., Saginaw, Michigan*, 48601, United States of America

As a participating institution in the Primary Breast Cancer Therapy Group (NSABP), we will contribute data from patients entering various group protocols. We are making contributions to Protocol 7, which evaluates L-PAM with L-PAM and 5-FU. The present application seeks funding (a) to permit continued patient accrual in ongoing protocols, and (b) to collect appropriate biological material and information relevant to such protocols. The new protocols are: (1) No. 6: A trial to compare the worth of segmental mastectomy with and without breast radiation with total mastectomy plus axillary dissection. All patients will undergo axillary dissection and those with histologically positive axillary nodes will receive adjuvant chemotherapy. (2) No. 8: A trial to compare the worth of three-drug chemotherapy (L-PAM, 5-FU and methotrexate) with that of two-drug chemotherapy (L-PAM and 5-FU). (3) No. 9: A trial to determine whether the antiestrogen tamoxifen, when combined with chemotherapy, improves the results obtained with chemotherapy alone. (4) No. 10: A trial to compare the value of the immunopotentiator C. parvum combined with chemotherapy vs. chemotherapy alone. (5) No. 11: A trial to evaluate various treatment modalities in the management of patients with Clinical Stage III breast cancer. In addition, the NSABP membership has decided, because of its unique composition, to implement adjuvant protocols for primary colorectal carcinoma. The group has the same capability to accomplish this as it has done for breast cancer. This institution will participate in such protocols.

Finally, another aim of this proposal is to enhance the multidisciplinary approach of this institution in clinical trials. Our institution (Saginaw Cooperative Hospitals, Inc.) is a good example of combined efforts in delivery of primary care by multidisciplinary approach. This approach is a standard procedure of our community for primary cancer therapy as well.

385. PRIMARY BREAST CANCER THERAPY GROUP

Poisson, R. C., Cote, J., Hopital St.-Luc, Surgical Oncological Service, *1058 St. Denis St., Montreal, Quebec*, H2X 3J4, Canada

The summary for this project is under entry no. 207.

386. NSABP INSTITUTIONAL GRANT APPLICATION

Breen, P. C., Beiler, D. D., Favino, C. J., Bernath, A. M., Fleetwood, M. F., Inst. for Medical Education & Research, Dept. of General Surgery, *Danville, Pennsylvania*, 17821, United States of America

We propose to continue active participation in the NSABP breast and bowel cancer protocol. Overall, we have been the fourth largest contributor of patients to these protocols as of 8/31/78. We are currently entering patients into NSABP protocols B-09, C-01, and R-01 and have institutional approval to begin patient entry into protocol B-06 which we plan to do immediately. In addition, we are following 67 living patients from protocols B-04 and B-08. The major objectives of the NSABP are to improve the disease free survival and quality of life for women with operable breast cancer and, more recently, for patients with colon or rectal cancer. The protocols evaluate the worth of techniques and modalities already employed (B-04); determine the value of the anti-estrogen drug Tamoxifen combined with chemotherapy and its relation to estrogen and progesterone receptors (B-09); test the efficacy of segmental mastectomy, with or without radiation, vs. more conventional surgery for survival cosmesis and study the significance of microscopic multifocal breast tumors (B-06). The rectal protocol (R-01) evaluates whether adjuvant chemotherapy or radiotherapy improves survival over surgery alone. The colon protocol (C-01) assesses the immunotherapy (BCG) vs. surgery alone. All of these protocols are designed to answer important questions about the biology and natural history of these cancers. The method of study is through prospective randomized closely monitored clinical trials.

387. NSABP INSTITUTIONAL GRANT - MOUNT SINAI HOSPITAL, CLEVELAND

Sachs, S. H., Bornstein, R. S., Berman, N. E., Goyal, R. K., Siegler, E. E., Karni, S., Reynolds, S. A., Hall, P. M., Mount Sinai Hospital of Cleveland, Division of Surgery, *University Cir., Cleveland, Ohio*, 44106, United States of America

The primary objective of the proposed research is to participate in prospective, randomized controlled clinical trials of the NSABP to assess the value of various therapeutic regimens when employed in the adjuvant setting. We will also participate in the testing of new therapies for such patients. An additional objective will be to participate in the collection of pertinent data from these trials to assist in the evaluation of present and new therapies. We will then disseminate the results of such clinical trials to the physicians in our institution and our community so that they better understand the need and justification for such studies and can then improve the care of their patients with breast cancer.

388. PRIMARY CANCER THERAPY GROUP

Lerner, H. J., DeLaurentis, D., Glassburn, J., Prasasvinichai, S., Olen, E., Pennsylvania Hospital, *8th & Spruce Sts., Philadelphia, Pennsylvania*, 19107, United States of America

As a participating institution in the Primary Breast Cancer Therapy Group (NSABP) we are contributing data from patients entered into the various group protocols. Patients have been entered into Protocol 5, which compared L-PAM with placebo; Protocol 7, which compared L-PAM with L-PAM and 5-FU; and Protocol 8, which compared the worth of 3 drug chemotherapy (L-PAM, 5-FU, and MTX) with a 2 drug chemotherapy (L-PAM and 5-FU). The present application seeks funding (a) to permit continued patient accrual in ongoing protocols, (b) to continue follow-up of patients entered into protocols which have terminated, and (c) to collect appropriate biological material and information relevant to such protocols. The new protocols are: (1) No. 6: A trial to compare the worth of segmental mastectomy with and without breast radiation with total mastectomy plus axillary dissection. All patients will undergo axillary dissection and those with histologically positive axillary nodes will receive adjuvant chemotherapy. (2) No. 9: A trial to determine whether the anti-estrogen Tamoxifen when combined with chemotherapy improves the results obtained with chemotherapy alone. (3) No. 10: A trial to compare the value of the immunopotentiator C. parvum combined with chemotherapy vs. chemotherapy alone. In addition, the NSABP membership has implemented adjuvant protocols for primary colo-rectal carcinoma. This institution participates in these protocols. Finally, an aim of this proposal is to enhance the multidisciplinary approach of this institution in clinical trials.

389. PRIMARY CANCER THERAPY GROUP (NSABP)

Elias, E. G., Didolkar, M. S., Morris, D. M., Kim, I., Toker, C., Bonczkowski, S., Soccio, J., Zentai, T., University of Maryland, Baltimore Professional Schools, School of Medicine, Dept. of Surgery, *655 W. Baltimore St., Baltimore, Maryland*, 21201, United States of America

As a participating member of the Primary Breast Cancer Therapy Group (NSABP) the University of Maryland and affiliated hospitals will contribute to ongoing and future proposed protocols, and provide the care and follow-up of patients entered in such protocols, and obtain necessary tissues for biological markers. The current proposal seeks funding to continue funded participation in the NSABP to: (a) Continue patient accrual at a more intense rate; (b) maintain follow up of the patients already entered into NSABP protocols; and (c) collect appropriate and necessary biological material. The University of Maryland currently participates in the following protocols: (1) B-06, which is a trial to compare the worth of segmental mastectomy with and without breast radiation with total mastectomy plus axillary dissection. All patients shall undergo axillary dissection and those with histologically positive lymph nodes will recieve adjuvant chemotherapy alone. (2) B-09, which is a trial to determine whether the anti-estrogen, Tamoxifen, when combined with chemotherapy, improves the results obtained with adjuvant chemotherapy alone. (3) B-07 and B-08 which are closed to patient entry. The principal investigator is the chairman of the Stage III breast cancer committee of the NSABP, which is developing a new protocol design for such license.

390. PRIMARY CANCER THERAPY GROUP

Economou, S. G., Wolter, J. M., Rush University, School of Medicine, Dept. of Surgery, *1725 W. Harrison St., Chicago, Illinois*, 60612, United States of America

This research involves participation as one of the institutions in the Primary Cancer Therapy Group (NSABP). The objectives of this group are to determine whether adjuvant treatment of patients with breast and bowel cancer can affect the subsequent course of the disease and the longevity of the patients. This application seeks funding (a) to permit uninterrupted follow-up of patients already entered into protocols which have complete accrual; (b) to permit continued patient accrual into ongoing protocols; (c) to collect appropriate biological material and information relevant to such protocols; and (d) to insure the continued intellectual participation of the investigators in this institution in the design and implementation of future studies.

Studies for which accrual is complete but data gathering continues include L-Pam vs. placebo, L-Pam alone vs. L-Pam plus 5-FU, L-Pam plus 5-FU vs. L-Pam, 5-FU and Methotrexate all in patients with Stage II breast cancer. Ongoing protocols for the same patient group include L-Pam and 5-FU vs. L-Pam, 5-FU and Tamoxifen or C. Parvum. A primary breast cancer study is examining segmental vs. total mastectomy with and without radiation.

A bowel adjuvant project is evaluating the effect of chemotherapy vs. immunoprophylaxis vs. surgery alone.

391. NATIONAL SURGICAL ADJUVANT PROGRAM FOR BREAST AND BOWEL

Foster, R. S., University of Vermont & State Agricultural College, School of Medicine, Dept. of Surgery, *85 S. Prospect St., Burlington, Vermont*, 05401, United States of America

As a participating institution in the Primary Breast and Bowel Cancer Therapy Group (National Surgical Adjuvant Project for Breast and Bowel Cancers, NSABP), we are con-

tributing data from patients entered into the various group protocols. We are currently following 87 patients already entered into protocols and anticipate entry of 20 to 30 new patients over the next 12 months.

392. SURGICAL ADJUVANT PROJECT FOR BREAST AND BOWEL CANCERS

Volk, H., Escher, G. C., Molnar, J. J., Ger, R., Flax, H., Carnevale, N., Kaplan, B. H., Pauporte, J., Stratford, F. A., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Surgery, *1300 Morris Park Ave., Bronx, New York*, 10461, United States of America

As a participating institution in the National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP), we are contributing data from patients entered into various Group breast and colon protocols. Our objectives are to evaluate the efficacy of modalities employed in the treatment of breast and colorectal cancers; to assess the worth of new and promising surgical adjuvant therapies prior to their general use; and to gather biologic and other pertinent data from patients with such cancers.

We have made major contributions to six previous breast cancer protocols and are committed to close patient follow-up. Ongoing protocols are: B-09 - A protocol to compare combined chemotherapy with and without Tamoxifen in the management of patients with surgically curable breast cancer; and C-01 - A clinical trial to evaluate postoperative immunotherapy and postoperative systemic chemotherapy in the management of resectable colon cancer.

As a result of the increasing capabilities of this Group, we are participating in protocol design for Stage I and Stage III breast cancer patients.

The present application seeks funding to permit continued patient accrual in ongoing and new protocols, continued follow-up of patients entered into protocols which have terminated, and to collect appropriate biological material and information relevant to such protocols.

Finally, an important aim of this proposal is to enhance the multidisciplinary efforts at this institution to clinical trials.

393. NATIONAL SURGICAL ADJUVANT PROJECT FOR BREAST AND BOWEL CANCERS (NSABP)

Fisher, B., University of Pittsburgh, School of Medicine, Dept. of Surgery, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

The National Surgical Adjuvant project for breast and bowel cancers (NSABP) is a multi-institutional (75 plus) cooperative cancer group with over 400 investigators conducting adjuvant breast and colo-rectal clinical trials. The group currently has 3 stage I and II breast cancer protocols open for entry which examine the merits of additive therapies such as chemotherapy, immunotherapy and anti-estrogens or more limited surgical procedures coupled with radiation therapy. The yearly accrual for 1978 will total about 900 patients and follow-up now has reached 4,500 patients who were entered into earlier surgical and chemotherapeutic trials.

All these efforts are reviving the National Cancer Institute's support in terms of Headquarters and institutional grants and contracts. In addition, we have enjoyed support from the American Cancer Society which has enabled us to fund new members until more adequate long-term funds could be secured and enabies us to carry out important but discrete projects such as monitoring estrogen/progesterone assay collection. The latter research was supported by the American Cancer Society developmental grant (RD-14) and has greatly strengthened our Tamoxifen (B-09) protocol by allowing us to scientifically monitor and perform quality assays on study patients.

In addition, the NSABP is about to analyze our first major surgical trial (B-04) at the five year point. We anticipate this report to be a major contribution to the surgical management of primary breast cancer. This would not have been possible without the American Cancer Society support we have received.

394. SURGICAL ADJUVANT PROJECT FOR BREAST AND BOWEL CANCERS

Desser, R. K., Bitran, J. D., Chiang, T. C., Hambrick, E., Michel, A. G., Recant, W., Michael Reese Hospital & Medical Center, Dept. of Medicine, *2929 S. Ellis Ave., Chicago, Illinois*, 60616, United States of America

The summary for this project is under entry no. 222.

395. NATIONAL SURGICAL ADJUVANT BREAST PROJECT

Fisher, B., University of Pittsburgh, School of Medicine, Dept. of Surgery, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

The summary for this project is under entry no. 214.

396. CANCER AND LEUKEMIA GROUP B

Holland, J. F., Wasserman, L. R., Cuttner, J., Aufses, A. H., City University of New York, Mount Sinai School of Medicine, Dept. of Neoplastic Diseases, *5th Ave. at E. 100th St., New York, New York*, 10029, United States of America

OBJECTIVES: A. To participate in the cooperative studies of the various therapeutic regimens in acute leukemia, chronic leukemia, multiple myeloma, the lymphomas, breast cancer, lung cancer, gastrointestinal cancer and other adult solid tumors to be studied by the Cancer and Leukemia Group B. B. The toxicity and therapeutic range of new agents will be determined in Phase I studies; the frequency, extent and duration of remission with new agents will be evaluated in the Phase II studies; and the relative efficacy of various therapeutic regimens at different stages of the disease will be determined in Phase III studies. C. To complete our development into a multidisciplinary group with full participation of surgeons and radiotherapists. This goal has been achieved with the participation of breast surgeons. We plan to extend this participation to general surgeons. D. To develop and participate in studies using immunotherapeutic agents in neoplastic disease states. E. To utilize the case material for the cooperative chemo- and radiotherapy studies for ancillary investigations of some of the biological, biochemical and immunological aspects of the neoplastic diseases under study.

BIBLIOGRAPHIC REFERENCES: Kyle, R.A., Gailani, S., Seligman, B.R., Blom, J., McIntyre, O.R., Pajak, T.F. and Holland, J.F.: Multiple Myeloma Resistant to Melphalan Treatment with Cyclophosphamide, Prednisone and BCNU. Cancer Treat. Rep. 63:1265-1269, 1979. Chahininan, A.P., Mandel, E.M., Holland, J.F., Jaffrey, I.S. and Terstein, A.S.: MACC (methotrexate, adriamycin, cyclophosphamide and CCNU) in Advanced Lung Cancer. Cancer 43: (No. 5) 1590-1597, 1979.

397. CANCER AND LEUKEMIA GROUP B - MEDICAL ONCOLOGY SUPPORT

Kennedy, B. J., Theologides, A., Bloomfield, C. D., Kiang, D., Vosika, G., Peterson, B., Frenning, D., Hrushesky, W., Hurd, D., Kostraba, N., Vogelzang, N., Shipman, G., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Medicine, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The Minnesota Oncology Group of the University of Minnesota Medical School is a participating member of the Cancer and Leukemia Cooperative Group B for the study of hematologic neoplasms and malignant solid tumors. The Minnesota Oncology group joined the CALGB in August of 1973.

Currently, the Minnesota Oncology Group consists of a Therapeutic Radiology component and participating members in the department of Laboratory Medicine and Pathology and the Department of Surgery. The Minnesota Oncology Group joined this cooperative group in order to provide patients with malignant diseases suitable for the cooperative studies conducted by the Cancer and Leukemia Group B. The Minnesota Oncology Group clinical material is composed primarily of patients with acute leukemia, lymphoma, breast cancer, gastrointestinal malignancies, lung cancer and a variety of miscellaneous tumors. The Minnesota Oncology Group consists of established investigators in malignant diseases employing chemotherapeutic agents and hormonal therapies.

The methods of study of diseases are the protocol programs established by the Cancer and Leukemia Group B. The Minnesota Oncology Group initiates new protocol concepts and pilot studies for the treatment of advanced malignant diseases, especially in the areas of lymphoma, leukemia, and solid tumors. The objectives of this research are the development of new chemotherapies and Phase I, Phase II, and Phase III evaluation of chemotherapy in the management of malignant diseases. The development and evaluation of such agents is best provided by cooperative studies that provide large numbers of patients and

long-term follow-up. Participation in clinical studies with Cancer and Leukemia Group B provides to that group a large source of clinical patients and investigators experienced in clinical evaluation of chemotherapeutic drugs.

BIBLIOGRAPHIC REFERENCES: Nissen, N.I., Pajak, T.F., Leone, L.A., Bloomfield, C., Kennedy, B.J., Ellison, R.R., Silver, R.T., Weiss, R.B., Cuttner, J., Falkson, G., Kung, F., Bergevin, P.R., and Holland, J.F.: Clinical trial of VP 16 -213 (NSC 141540) i.v. twice weekly in advanced neoplastic disease (Study by the Cancer and Leukemia Group B). Cancer 45: 232-235, 1980.

398. HUMAN RADIATION CARCINOGENESIS STUDY

Woodard, E. D., University of Rochester, School of Medicine & Dentistry, Dept. of Radiology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

This represents a continuation of a long-term prospective study of radiation-induced carcinogenesis in three human populations: the first, persons who were treated in infancy with x-rays for alleged enlargement of the thymus gland; the second, women who received x-ray treatments to the breasts for postpartum mastitis; and the third, persons given x-ray and/or radium treatments to the head in early childhood for lymphoid hyperplasia of the nasopharynx.

Health data are collected by mail questionnaires from treated persons and from their untreated sibling controls. Significant reported illnesses are verified through the attending physician and hospital. Histological reviews are performed on slides from tumors of primary interest in the studies.

A program of mammographic-thermographic screening of the women who received breast irradiation will be repeated. In addition, a sample of their untreated sisters (controls) who meet NCI recommended eligibility requirements for mammographic-thermographic screening will also be examined.

The objectives of the program are (1) to determine the qualitative nature and quantitative risk of radiation-induced neoplastic disease and of conditions with abnormal immunological features, and (2) to effect, by screening, the early diagnosis and treatment of breast cancer in a high-risk population.

BIBLIOGRAPHIC REFERENCES: Shore, R.E., Hempelmann, L.H., Kowaluk, E., Mansur, P.S., Pasternak, B.S., Albert, R.E., and Haughie, G.E., Breast Neoplasms in Women Treated with X-rays for Acute Post-Partum Mastitis, JNCI, 59, 813-822, 1977.

399. RADIATION THERAPY ONCOLOGY GROUP

Perez, C. A., Marks, J., Phillips, G., Purdy, J. A., Simpson, J., Washington University, School of Medicine, Dept. of Radiology, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

The summary for this project is under entry no. 194.

400. ADJUVANT THERAPY OF BREAST CANCER

Jerry, L. M., Geggie, P. H., Russell, J., Arthur, K., Pow, R. E., Francis, J. R., Alberta Provincial Cancer Hospitals Board, *2104 2nd St. SW, Calgary, Alberta, Canada*

The summary for this project is under entry no. 77.

401. PHASE II STUDY OF CHLOROZOTOCIN

Spaulding, M. B., Noyes, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

The summary for this project is under entry no. 314.

402. SOUTHWEST ONCOLOGY GROUP

Vaughn, C. B., Caoili, E., Chen, S., Leitchman, D., Cyrowski, G., Young, S. C., Puri, K., Providence Hospital, Dept. of Oncology, *16001 W. Nine Mile Rd., Southfield, Michigan*, 48075, United States of America

Studies using the multimodality approach will be designed and piloted before presenting to the Southwest Oncology Group (SWOG) for group-wide protocol evaluation and approval. A protocol is now being reviewed for group-wide study consideration in the multimodality treatment of Stage III breast cancer. A similar study for the treatment of localized advanced cancer of the distal esophagus using pre-op radiation and pre-op high dose methotrexate with citrovorum rescue followed by surgery is being designed. The patient will receive six months to a year of adjuvant HDMTX/CR. Another study which includes the estrogen receptor and progesterone receptor will be performed on a variety of cancers. Yet another study is designed to study the molecular form of receptors in breast cancer using the ultracentrifugation and isoelectric focusing technique. An association of the molecular forms in the receptor has been designed and is now tested with adriamycin and VP-16 in disseminated breast cancer. This is a very interesting combination for second line chemotherapy in patients with disseminated breast cancer who are failing or relapsing on Cooper's (CMEVP).

The patient population represents diverse socioeconomic groups where there is a wide variety of cancers. The principal investigator, associate oncologist, and hematologist will provide consultative services for malignant diseases to the inner-city hospitals. They also will provide a teaching source for inner-city oncological teaching programs and tumor boards. We look forward to another progressive year.

403. SOUTHWEST ONCOLOGY GROUP

Fletcher, W. S., Vetto, R. M., Paxton, H. D., Goodnight, S. H., Oregon State Higher Education System, University of Oregon Health Sciences Center, School of Medicine, Dept. of Surgery, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon*, 97201, United States of America

OBJECTIVES: 1. To combine the disciplines of Surgical Oncology, Medical Oncology, Radiation Oncology, Pathology, and Immunology in a truly synergistic attack on the clinical cancer problem. 2. To participate in Southwest Oncology Group phase I, II, III, and adjuvant studies. 3. To conduct preclinical pilot studies for possible use by the Southwest Oncology Group. 4. To conduct clinical pilot studies for possible use by the Southwest Oncology Group. 5. To provide core laboratory support and suitable administrative facilities for the clinical evaluation of various techniques to predict response to endocrine ablation in breast and other cancers. 6. To utilize Southwest Oncology Group studies to link basic science to modern clinical care within the area as an educational mechanism.

404. SOUTHWEST ONCOLOGY GROUP PROTOCOL 7809, MAYTANSINE (NSC-153858) THERAPY OF ADVANCED BREAST CANCER, PHASE II

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

The summary for this project is under entry no. 339.

405. SWOG 7732, CMF WITH AND WITHOUT TAMOXIFEN IN PATIENTS WITH ESTROGEN RECEPTOR POSITIVE BREAST CANCER, PHASE III STUDY

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

The summary for this project is under entry no. 235.

406. SOUTHWEST ONCOLOGY GROUP 7725 - CMPF CHEMOTHERAPY PLUS LEVAMISOLE FOR BREAST CANCER (ABBREV)

Coltman, C. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *San Antonio, Texas*, 78284, United States of America

The summary for this project is under entry no. 340.

407. A BREAST REGISTRY IN NORTHERN ALBERTA WITH RESEARCH AND CLINICAL APPLICATIONS

Burns, P. E., Lees, A. W., Grace, M. G., Dr. W.W. Cross Cancer Inst., Dept. of Radiation Oncology, *11560 University Ave., Edmonton, Alberta*, T6G 1Z2, Canada

A breast registry was created in Northern Alberta to study the aetiology, epidemiology, diagnosis, treatment, and survival patterns of malignant and benign breast tumors. About 700 patients with benign conditions and 250 with newly diagnosed breast cancer attend the breast clinics at the Cross Institute each year. Interview data are collected from all patients, who represent 90% of all breast cancer registrations and about 30% of women treated for benign breast disease. More than half of all patients registered with breast cancer are assessed pre-operatively at these clinics by one of two clinicians. Data from the registry have been used to compare diagnostic accuracy, to

study incidence trends, to assess the influence of exogenous hormones and other aetiologic factors, to compare 1968 and 1973 UICC staging and to determine factors related to survival of breast cancer patients.

408. EASTERN COOPERATIVE ONCOLOGY GROUP
Lerner, H. J., Zaren, H., Pennsylvania Hospital, Section of Surgical Oncology & Cancer Chemotherapy, *8th & Spruce Sts., Philadelphia, Pennsylvania*, 19107, United States of America

The summary for this project is under entry no. 79.

409. CALGB PROTOCOL 7682 - COMBINATION CHEMOTHERAPY IMMUNOTHERAPY OF METASTATIC, RECURRENT, OR INOPERABLE CARCINOMA OF THE BREAST
Spaulding, M. B., Henderson, E. S., Sanani, S., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *3495 Bailey Ave., Buffalo, New York*, 14215, United States of America

The summary for this project is under entry no. 284.

VI. CANCER CONTROL PROGRAMS INCLUDING SCREENING, TEACHING, AND DEMONSTRATION PROGRAMS

A. PROTOTYPE NETWORK DEMONSTRATION PROJECTS IN BREAST CANCER

410. PROTOTYPE NETWORK DEMONSTRATION PROJECT IN BREAST CANCER
Marchant, D. J., New England Medical Center Hospital, *171 Harrison Ave., 7701 Burholme Ave., Boston, Massachusetts*, 02111, United States of America

This contract is designed to establish a regional network of community hospitals as a demonstration program to the medical community for the utility and need of an organized and multidisciplinary approach to the total care of breast cancer patients.

411. PROTOTYPE NETWORK DEMONSTRATION PROJECT IN BREAST CANCER
Engstrom, P. F., Inst. for Cancer Research, *Philadelphia, Pennsylvania*, 19111, United States of America

The Contractor shall commence with the implementation stage of his prototype network demonstration project in breast cancer.

412. PROTOTYPE NETWORK DEMONSTRATION PROJECT IN BREAST CANCER
Maddox, W. A., University of Alabama in Birmingham, School of Medicine, Dept. of Surgery, *1919 7th Ave. S., Birmingham, Alabama*, 35233, United States of America

The contractor shall organize a network of cooperating hospitals to develop and implement comprehensive cancer control activities in their community relating to the diagnosis, staging, treatment, and rehabilitation of all stages of cancer of the female breast. The contractor shall serve as the major cancer hospital to which the network shall be linked.

413. PROTOTYPE NETWORK DEMONSTRATION PROJECT IN BREAST CANCER
Maurer, L. H., Dartmouth College, School of Medicine, Dept. of Medicine, *P.O. Box 833, Hanover, New Hampshire*, 03755, United States of America

The Contractor shall commence with the implementation stage of his prototype network demonstration project in breast cancer.

414. PROTOTYPE NETWORK DEMONSTRATION PROJECT IN BREAST CANCER
Whitney, L. W., Wilmington Medical Center, *501 W. 14th St., Wilmington, Delaware*, 19899, United States of America

The Contractor shall commence with the implementation stage of his prototype network demonstration project in breast cancer.

415. PROTOTYPE NETWORK DEMONSTRATION PROJECT IN BREAST CANCER
Acker, S. E., Oklahoma Medical Research Foundation, *825 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

OBJECTIVES: To improve end results of breast cancer management and treatment. To extend currently available treatment regimens to outlying regional medical centers.

APPROACH: To improve early diagnosis of breast cancer through increased utilization of screening centers, training nurse professionals in cancer detection, and teaching women breast self-examination; to improve primary therapy through rapid dissemination of information gleaned from clinical research protocols that have proven to be effective; to stimulate a rational approach to determination of treatment regimens through a multidisciplinary team effort and avoidance of stereotyped automatic treatment choice; to improve treatment of advanced disease.

The project has been active for three years and has shown a 50% increase in case accrual with marked shift toward earlier diagnosis; the separation and timing of biopsy and treatment are being increasingly utilized; proper patient screening and evaluation prior to determining therapeutic approaches are gaining rapid approval.

416. NETWORK DEMONSTRATION PROJECT IN BREAST CANCER
Foster, R. S., University of Vermont & State Agricultural College, School of Medicine, Dept. of Surgery, *85 S. Prospect St., Burlington, Vermont*, 05401, United States of America

OBJECTIVES: 1. Continue entry of breast cancer patients into project registry. We also plan to continue beyond time of funding under this contract to assess long-term aspects of BSE program. 2. Compare clinical and pathological stages of breast cancer in patients taught BSE during Network Project with those in patients not taught BSE during project. 3. Continue to assess physician records and physician management of breast cancer patients. 4. Evaluate educational materials. 5. Assess impact of public education on BSE performance.

417. DEMONSTRATION PROJECT IN BREAST CANCER
Horton, J., Union University, Albany Medical College, School of Medicine, Dept. of Medicine, *47 New Scotland Ave., Albany, New York*, 12208, United States of America

The purpose of this contract is to organize a network of cooperating hospitals to develop and implement comprehensive cancer control activities in the community relating to the diagnosis, staging, treatment, and rehabilitation of all stages of cancer of the female breast. The Contractor will be the center to which the participating hospitals are linked. The objectives of this effort is to improve case management, develop approaches in case management to be applied in a high proportion of patients in defined populations, establish mechanism of case delivery, develop pathways for decision-making, and develop management approaches which can be used in the community.

418. A PILOT DEMONSTRATION DETECTION PROGRAM
Greco, V. F., Community Cancer Corp. of Luzerne County, *Box 1345, Wilkes-Barre, Pennsylvania*, 18703, United States of America

This pilot detection program is the first effort in implanting a cancer control plan, begun by area physicians several years ago and supported in part by a Cancer Center Planning grant. The pilot proposes to use specially trained nurse clinicians to perform screening tests and examinations in Luzerne County, Pennsylvania. During the three-year program, nurses will be recruited from the community and trained at Hahnemann Oncologic Institute, and they will perform complete screening examinations in two-hospital based clinics. A projected population of 10,944 people over the age of 40 will be screened for cancer of the mouth, throat, cervix, prostate, breast, skin, and rectum.

Demonstration pilot efforts include the training and utilization of nurse clinicians in this unique fashion, studying variables in patient participation, acceptance of nurse clinicians by both patients and physicians, examining the validity and reliability of this form of community based cancer screening, analyzing cost variables and the progressive development of programmatic self-support by the community. The pilot is further designed to encourage the introduction of a single county tumor registry

and to encourage additional epidemiologic research in future years.

The applicant is the Community Cancer Corporation of Luzerne County (CCC), a new non-profit corporation which has been created to plan and manage this and other cancer related service projects. The corporation and indeed this pilot request are an outgrowth of the extremely high incidence of cancer in the county, the high degree of physician and community support for the project and the potential applicability of the pilot to other similar regions of the country.

419. CANCER CONTROL DEVELOPMENTAL GRANT

Robbins, G. F., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

The Cancer Control Developmental Program at Memorial Sloan-Kettering has four objectives for its renewal over the next three years. They are: 1) To expand the present pilot cancer data system to include 20 hospitals over a three-year period; 2) to develop educational, treatment, and evaluation programs that focus on breast cancer; 3) to improve radiation therapy planning in the New York metropolitan area, particularly those hospitals affiliated as cooperating hospitals in this cancer control demonstration project; and 4) to expand educational programs in the surrounding community in the field of cancer control by means of programs supported and not supported by the National Cancer Institute.

B. TEACHING TECHNIQUES FOR BREAST CANCER SCREENING AND DETECTION

420. SIMULATED BREASTS FOR THE TRAINING OF LUMP DETECTION

Pennypacker, H. S., Hench, L. L., Adams, C. K., Goldstein, M. K., Stein, G. H., Lynch, M. A., State University System of Florida, University of Florida, Center for Ambulatory Studies, *238A Tigert Hall, Gainesville, Florida*, 32611, United States of America

The overall objective of this project is to determine, with the aid of accurate models of the human breast, the most efficient and effective method of training the manual skills required for lump detection. Studies to date have substantially advanced the state of the art of breast simulation, resulting in models which simulate natural granularity and contain movable lumps of variable size and hardness. An automated training technology providing instruction and immediate feedback for approximation to the correct method of palpation will be completed and deployed in a field validation study involving 5,000 women. Data from this study will include records of lumps actually detected as a result of training provided. Concurrently, studies in progress will determine the proper frequency of home practice to maintain proficiency, the role of simple models in maintaining home practice, and the extent to which naturally occurring tissue change can serve a functional role in home practice.

BIBLIOGRAPHIC REFERENCES: Madden, M. C., Hench, L. L., Hall, D. C., Adams, C. K., Goldstein, M. K., Pennypacker, H. S., and Stein, G. H. Development of a model human breast with tumors for use in teaching breast examination. Journal of Bioengineering 1978, Vol. 2, 427-435. Stephenson, H. S., Hall, D. C., Adams, C. K., and Pennypacker, H. S. The effects of certain training parameters on detection of simulated breast cancer. Journal of Behavioral Medicine, 1979, Vol. 2, No. 3, 239-250.

C. BREAST CANCER CLINICS, SCREENING AND DETECTION CENTERS

421. EARLY DETECTION OF BREAST CANCER

Guiss, L. W., University of Southern California, School of Medicine, Dept. of Surgery, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

OBJECTIVE: Continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women will continue to be rescreened on a projected annual basis by means of three screening modalities: mammography, thermography, and physical examination.

422. SCREENING FOR EARLY DETECTION OF CANCER OF THE BREAST

Fisher, B., University of Pittsburgh, School of Medicine, Dept. of Surgery, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

Eighteen-month extension of the Breast Cancer Demonstration Project: The Contractor has continued to rescreen approximately 10,000 women each year. This extension provides for the final fifth year screening visit and for phaseout of the project. The Contractor will rescreen approximately 5,370 women and will concentrate on data correction and validation in the final six-month period of this contract extension.

423. SCREENING FOR DETECTION OF BREAST CANCER

Gilbert, F. I., Pacific Health Research Inst., *Alexander Young Bldg., Suite 542, Honolulu, Hawaii*, 96813, United States of America

The summary for this project is under entry no. 14.

424. SCREENING FOR EARLY DETECTION OF CANCER

Young, D. C., Iowa Lutheran Hospital, *University at Penn. Ave., Des Moines, Iowa*, 50316, United States of America

Eighteen-month extension of the Breast Cancer Detection Demonstration Project: The Contractor has continued to rescreen approximately 10,000 women each year. This eighteen-month extension provides for the final fifth year screening visit and for phaseout of the project. The Contractor will rescreen approximately 5,060 women and will concentrate on data correction and validation in the final six-month period of this contract extension.

425. EARLY DETECTION OF CANCER OF THE BREAST

Threatt, B., University of Michigan, Ann Arbor Campus, Medical School, Dept. of Radiology, *1335 E. Catherine St., Ann Arbor, Michigan*, 48104, United States of America

Eighteen-month extension of the Breast Cancer Detection Demonstration Project: The Contractor has continued to rescreen approximately 10,000 women each year. This eighteen-month extension provides for the final fifth year screening visit and for phaseout of the project. The Contractor will rescreen approximately 7,000 women and will concentrate on data correction and validation in the final six-month period of this contract extension.

426. EARLY DETECTION OF CANCER OF THE BREAST

Shnider, B., Georgetown University, School of Medicine, Dept. of Neurology, *3800 Reservoir Rd. N.W., Washington, District of Columbia*, 20007, United States of America

One-year renewal of Breast Cancer Detection Demonstration Project: Contractor will continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women will continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination - in accordance with the contract statement of work, and NCI/ACS issured screening guidelines.

427. PROGRAM FOR DETECTING CANCER OF THE BREAST

Isard, H. J., Albert Einstein Medical Center, *York & Tabor Rds., Philadelphia, Pennsylvania*, 19141, United States of America

One-year renewal of Breast Cancer Detection Demonstration Project: Continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women will continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination - in accordance with the contract statement of work, and NCI/ACS issued screening guidelines.

428. SUPPORT OF CANCER-DETECTION PROGRAM

Rodes, N. E., Cancer Research Center, *Garth Ave. & Hwy. 40, P.O. Box 1268, Columbia, Missouri*, 65201, United States of America

Eighteen-month extension of the Breast Cancer Demonstration Project: The Contractor has continued to rescreen approximately 10,000 women each year. This extension provides for the final fifth year screening visit and for phaseout of the project. The Contractor will rescreen approximately 5,500

women and will concentrate on data correction and validation in the final six-month period of this contract extension.

429. BREAST CANCER DETECTION DEMONSTRATION PROJECTS

Rodes, N. E., Cancer Research Center, *Garth Ave. & Hwy. 40, P.O. Box 1268, Columbia, Missouri,* 65201, United States of America

OBJECTIVES: Collect 30 cc's of blood in clot tubes from Breast Cancer Demonstration Project screenees. Prepare the serum fraction from each blood sample and rapid-freeze such sera. Store serum samples prior to shipment, and record any temperature deviations during storage. Periodically ship the appropriate serum samples to NCI designated bank facility under conditions designated to prevent sample thawing. Maintain accurate records for sample acquisition, coding, and processing. Provide definitive diagnosis of the pathology of the breast lesion(s) and the status of each patient. Allow access to specimen slides and blocks for review of pathologic findings. Prepare and forward the clinical information form for each patient whose serum has been sent to the bank facility. Establish evaluation mechanisms and standards, and assure that all program objectives are achieved. Collect one 30 ml postoperative specimen from post-biopsy cases within the first month and process it in the same manner.

430. BREAST CANCER DETECTION DEMONSTRATION PROJECT

McClaw, M. V., St. Vincent's Medical Center, *Barrs St. & St. Johns Ave., Jacksonville, Florida,* 32204, United States of America

One-year renewal of breast cancer detection demonstration project: Contractor will continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women will continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination - in accordance with the contract statement of work and NCI/ACS issued screening guidelines.

431. BREAST CANCER DETECTION DEMONSTRATION PROJECT

Moskowitz, M., University of Cincinnati, School of Medicine, Dept. of Radiology, *Eden & Bethesda Aves., Cincinnati, Ohio,* 45221, United States of America

Six-month extension of the Breast Cancer Detection Demonstration Project: The Contractor has continued to rescreeen approximately 10,000 women each year. This six-month extension provides for phaseout of the project. The phaseout plan is for the Contractor to screen approximately 1,300 women during the first three months of the extension period and perform data correction and validation during the entire six-month period.

432. BREAST CANCER DETECTION DEMONSTRATION PROJECT

Constantine, H. P., Rhode Island Hospital, *593 Eddy St., Providence, Rhode Island,* 02903, United States of America

The Contractor will continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women wil continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination, in accordance with the contract statement of work and NCI/ACS issued screening guidelines.

433. BREAST CANCER DETECTION DEMONSTRATION PROJECTS

Hartmann, W. H., Vanderbilt University, School of Medicine, Dept. of Pathology, *21st Ave. S. & Garland, Nashville, Tennessee,* 37232, United States of America

Contractor will continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women will continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination.

434. BREAST CANCER DETECTION DEMONSTRATION PROJECT

Ingram, M. D., Vanderbilt University, School of Medicine, Dept. of Radiology, *21st Ave. S. & Garland, Nashville, Tennessee,* 37232, United States of America

Eighteen-month extension of the Breast Cancer Demonstration Project: The Contractor has continued to rescreen approximately 10,000 women each year. This extension provides for the final fifth year screening visit and for phaseout of the project. The Contractor will rescreen approximately 8,000 women and will concentrate on data correction and validation in the final six-month period of this contract extension.

435. BREAST CANCER DETECTION DEMONSTRATION PROJECT

Present, A. J., University of Arizona, School of Medicine, Dept. of Radiology, *1501 N. Campbell Ave., Tucson, Arizona,* 85721, United States of America

OBJECTIVE: Continue to rescreen as many as possible of an original number of ten thousand women participating in this project. These women will continue to be rescreened on a projected annual basis by means of three screening modalities - mammography, thermography, and physical examination - in accordance with the contract statement of work, and NCI/ACS issued screening guidelines.

436. BREAST CANCER DETECTION DEMONSTRATION PROJECT

Goodman, M. J., Good Samaritan Hospital & Medical Center, *1015 N.W. 22nd Ave., Portland, Oregon,* 97210, United States of America

Contractor shall screen 5,000 women annually in the age group 35-75 in accordance with NCI Protocol. The screening will consist of history, clinical examination, thermography, and mammography. The purpose of the screening is the earlier detection of breast cancer. Examination reports are to be provided in accordance with NCI instructions. Close liaison is to be maintained with the American Cancer Society to ensure that agency's support of the project.

437. STUDIES OF THERAPEUTIC END RESULTS AND PROGNOSTIC FACTORS

Myers, M. H., Stanek, E. J., Hankey, B. F., Prorok, P. C., Chen, J. S., Heise, H. W., Connelly, R. R., Baranovsky, A., Silverman, D. T., Devesa, S. S., Steinhorn, S. C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Biometric Research & Analytic Studies Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Ten-year follow-up results from the HIP study of screening for breast cancer have shown that the screened group experienced 1/3 less mortality from breast cancer than the control group. This reduction appeared to be concentrated in women over 50. The associations of cancer incidence with income and education were studied. Among whites, strong negative associations were observed for esophageal, stomach, lung and cervical cancer, with positive associations for colon, bladder and breast cancer. An analysis of TNCS and SEER data showed that for white males the incidence rate of mesothelioma has increased in recent years. The development of methodology for the evaluation of screening programs has demonstrated new age dependent characteristics of lead time and length bias. Appropriate variables to use in the analysis of randomized screening trials were defined. A study of suicides among cancer patients indicated that male patients were at twice their expected risk of suicide while females were not at excess risk. The relationship of the levels of selected urinary steroid metabolites to breast cancer recurrence subsequent to radical mastectomy was studied: relationships were observed only for postmenopausal patients.

BIBLIOGRAPHIC REFERENCES: Cutler, S.J., Myers, M.H., Steinhorn, S.C., and Flannery, J.T.: Gains in cancer treatment in the 1970's. Tufts Medical Alumni Bulletin, Tufts University School of Medicine, Medical Alumni Weekend and Reunion Days, Boston, Massachusetts, April 26-29, 1979. (In Press). Li, F.P., Myers, M.H., Heise, H.W. and Jaffee, N.: The course of 5-year survivors of childhood cancer. The J. Pediatr. 93: 185-187, 1978.

438. CLINICAL ONCOLOGY (MULTIDISCIPLINARY)

Carbone, P. P., University of Wisconsin, Madison Campus, Center for the Health Sciences, Dept. of Human Oncology, *500 Lincoln Dr., Madison, Wisconsin*, 53706, United States of America

Projects included in this program focus on the natural history, causation, detection, and experimental treatment of solid tumors, stressing use of chemotherapeutic drugs and modulators of the immune and endocrine systems. Clinical trials for breast and pancreatic tumors; causation, early detection and intravesical treatment of bladder tumors; analysis of bony metastasis and hypercalcemia in breast and prostate cancers; in vitro and clinical immunological effects of levamisole and interferon; and pharmacology and clinical efficacy of platinum-containing coordination compounds and antiestrogens comprise studies under way.

The program depends on interdisciplinary collaboration of laboratory and clinical investigators, biostatisticians, and data management experts devoted to an integrated, interactive effort.

BIBLIOGRAPHIC REFERENCES: Tormey, D.C., and Carbone, P.P. What is the optimum number of agents? Int. J. Radiation Oncology Biol. Phys. 4: 301-303, 1978. Davis, T.E., and Carbone, P.P. Drug treatment of breast cancer. Drugs 16: 441-464, 1978.

439. DATA MANAGEMENT CENTER FOR BREAST CANCER DETECTION

Foradori, G., University City Science Center, *3624 Market St., Philadelphia, Pennsylvania*, 19104, United States of America

The summary for this project is under entry no. 15.

440. THE GUERNSEY TRIAL

Hayward, J. L., Bulbrook, R. D., Gravelle, H., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, c/o St. Bartholomew's Hospital, London WC2A 3PX, England, United Kingdom*

Nearly 2000 women have now taken part in the new trial on the island of Guernsey to compare blood and urine hormone levels with mammographic findings in normal women. Each month, early morning and 24-hour urine specimens plus a 50 ml blood sample are taken from 100 women aged over 35. Subsequently, each woman has a mammographic and clinical examination of both breasts. The clinical examination is being undertaken by one of the surgeons on the island (J. Dickson, A.B. Seth-Smith, C. Rey, R.H. Allsopp, T. Peet, J. Ferguson), and the mammographic examination is being undertaken at the Princess Elizabeth Hospital by Dr. J. Bulstrode. At three-month intervals, the mammograms are being independently reviewed and categorized according to factors reported to indicate high risk (Wolfe, Cancer, 1976. 37, 2486). Five thousand women will be entered into the trial over a period of five years and eventually the mammographic and endocrine findings will be compared. In addition, a detailed history is being taken from each woman, and data from this will be compared with the radiographic, clinical and enodocrinological findings.

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